Malignant Tumors of the Trachea

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Malignant Tumors of the Trachea

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Contents

CHAPTER ONE

General Introduction

The Trachea

The trachea is a pipe-shaped conduit for the passage of air and secretions between the larynx and the lungs [1], hence the term "windpipe" that is used in popular speech (Figure 1). The length of the trachea in the adult male ranges from 10 to 13 cm from the lower border of the cricoid cartilage superiorly to the top of the carina caudally, fortified with about two C-shaped cartilage rings every centimeter [2]. The trachea runs through both the neck and the chest. The upper part of the trachea is almost subcutaneously located anterior in the midline of the neck [1] in close relationship to the thyroid gland anteriorly and the pharyngo-esophageal junction posteriorly. The lower part of the trachea is located in the upper mediastinum behind the superior part of the sternum and adjacent to the esophagus posteriorly.

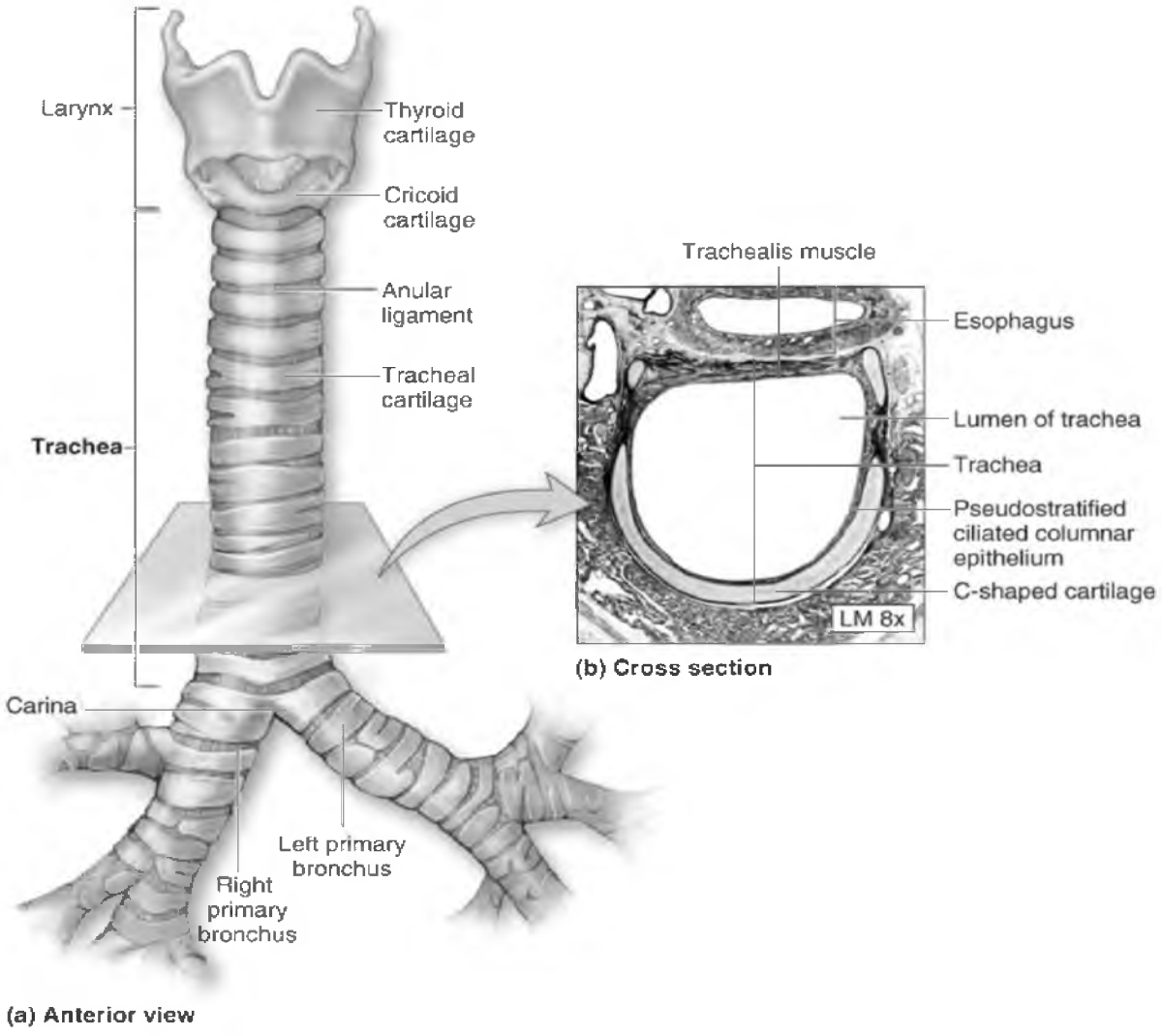

Figure 1. The adult trachea. Printed with permission from McGraw-Hill

When it comes to surgical procedures of the trachea, this dual localization makes the trachea part of the work fields of both thoracic surgeons and head and neck surgeons. Which specialty takes care of the trachea is mostly center dependent. In some centers, the thoracic surgeon is experienced with both intrathoracic tracheal and higher laryngotracheal resections, in other centers the head and neck surgeon does not evade mediastinal tracheal resections, and in some centers the thoracic surgeon and head and neck surgeon cooperatively perform tracheal surgery. An example of a cooperative surgical relationship is the Radboud University Medical Centre St Radboud in Nijmegen, the Netherlands. In this centre, patients with trachea-related disease are managed by a multidisciplinary team consisting of a pulmonologist, radiologist, radiotherapist, thoracic surgeon and head and neck surgeon.

Primary Tracheal Tumors

One of the most important and difficult conditions managed by this multidisciplinary team is cancer of the trachea. Usually, this is either a primary carcinoma of the trachea or a thyroid carcinoma growing directly into the trachea.
Although the trachea is lined with respiratory epithelium like the larynx and the bronchi and shares smoking as an important risk factor [3-5], tracheal cancer is very rare and occurs 40 times less frequent than laryngeal cancer and 400 times less frequent than bronchial cancer [3,5-7]. This distinct difference in incidence is mainly attributed to the laminar airflow in the trachea, as a result of which less carcinogens might be deposited in the tracheal mucosa compared with the mucosa of the larynx and bronchi [8].

Tracheal Surgery

The first tracheal resection and reconstruction was done by Küster in 1886 [9]. This was however a limited resection of a short segment of benign stenosis of cervical trachea.
Before single-staged tracheal resection and reconstruction became a feasible operation in a wider category of diseases, patients were mostly offered a permanent tracheostomy or airway tube. In some cases, staged procedures were employed to reconstruct the trachea using a wide variety of materials; foreign materials, nonviable tissue, autogeneous tissue, tissue engineering and allogeneous transplantation [10]. Most of these techniques were technically difficult, had a high rate of complications and were successful in few selected cases only. It was not until the fifties and sixties of the twentieth century that single-staged tracheal resection and reconstruction really took off. Grillo (Figure 2) and co-workers [2] and Salassa and associates [11] described the blood supply to the trachea. The surgical technique was adapted so that the lateral blood supply was not impeded while dissecting around the trachea.

Figure 2.
Hermes C. Grillo, M.D.

Grillo and Pearson and their co-workers further developed techniques of mobilization by which up to around 50% of tracheal length could be resected without excessive anastomotic tension [2,12-16]. Since, segmental tracheal resection is a safe airway-preserving surgical technique with good results and low morbidity and mortality [17,18].

Thyroid Carcinoma with Tracheal Involvement

Thyroid carcinoma is a relatively common tumor, occurring in approximately 3 per 100,000 persons in the Netherlands [19] and 14 per 100,000 persons in the United States [20]. In the United States, thyroid carcinoma was the sixth leading site of new cancer cases in 2008 [20]. Although death in thyroid carcinoma is uncommon, more than half of all deaths in well and poorly differentiated thyroid carcinoma is caused by airway obstruction or bleeding [21].
Thyroid carcinoma is usually treated with surgical resection in combination with non-surgical management. The invasion of larynx or trachea occurs in approximately 6% of all patients with thyroid carcinoma. It is however very unusual to find tracheal involvement preoperatively, and thus the operative planning is often not aimed at airway surgery. In more than 80% of cases, adherence or invasion of the trachea or larynx is found intra-operatively by the surgeon performing thyroidectomy [22]. Controversy exists on how the surgeon should deal with this finding. One of the methods to remove the disease is to scrape or "shave" off the thyroid carcinoma attached to the airway [22-25], while some authors state that this procedure violates oncologic principles [26,27], favoring en bloc resection of the thyroid carcinoma in conjunction with the involved airway segment [21,28-31].

Aims and Scope of this Thesis

This thesis aims to describe the treatment of patients with tracheal cancer and the outcome on a population-based level. The epidemiology, histology, presentation, diagnosis, and management of primary tracheal cancer will be discussed in more detail in **Chapter 2**. Despite the very low incidence of malignant tumors of the trachea, two large patient series were investigated at the Massachusetts General Hospital (Boston, MA), affiliated with Harvard Medical School (Cambridge, MA). This center is one of the world's leading institutes with the largest experience in tracheal

surgery available. The results from these series attribute to the knowledge of and clinical decision making in the two most common histologic types of primary tracheal carcinoma (**Chapters 3.1 and 3.2**).

As shown in Chapter 2, there is an important discrepancy in the treatment of primary tracheal cancer between population-based studies [4,5,32] and surgical series [33,34]. In this thesis, we try to elucidate the cause for this discrepancy. In **Chapter 4.1**, the situation regarding the treatment of tracheal cancer in the Netherlands is mapped and the nationwide results of all applied treatment modalities are given for a 14-year period. Next, **Chapter 4.2** describes a uniquely designed nationwide audit by a multidisciplinary team of experts that was undertaken in the Netherlands to answer the question what proportion of patients with primary tracheal carcinoma can be candidates for surgical resection. Both studies were performed in collaboration with the Netherlands Cancer Registry.

An extensive overview of the controversy in the literature on thyroid carcinoma invading the airway, supplemented with a review of the epidemiology, characteristics, presentation, diagnosis and staging of thyroid carcinoma invading the larynx or trachea is given in **Chapter 5.1**. In **Chapter 5.2**, the operative results and long-term survival and disease-free survival results in patients with thyroid carcinoma invading the airway treated with segmental airway resection are discussed, and an analysis is made of the difference in outcome between patients managed with limited “shave” resection versus patients undergoing en bloc resection including tracheal resection.

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CHAPTER TWO

Clinical Aspects and Treatment of Primary Tracheal Malignancies

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ABSTRACT

Objective: Primary tracheal tumors pose a diagnostic and therapeutic challenge for the physician when confronted with this mostly malignant tumor. Diagnosis is often delayed for months or years due to its aspecific and asthma-mimicking symptoms. Knowledge from retrospective series is limited and few clinicians have gained experience with this tumor. The available literature on the diagnosis and management of this group of tumors is reviewed to summarize the available knowledge about these uncommon tumors. New diagnostic, staging and treatment guidelines are proposed.

Methods: PubMed was searched for English publications from 1960. The available literature was reviewed and summarized.

Results: Surgical resection and primary reconstruction is the best curative treatment modality available at present. In centers of experience, more than half of all patients with tracheal cancer may be candidates for surgical resection, although in population-based studies this treatment is applied in only 10-25% of patients.

Conclusions: Selecting patients that are candidates for surgical treatment is important in the workup of patients with tracheal cancer. Toward this goal, centralization of care concerning tracheal tumors is advised. Centralization may increase long-term survival and decrease operative morbidity and mortality even further.

Introduction

Most tracheal tumors are malignant [1], and thus threaten the patient's life not only by airway obstruction, but by locoregional invasion and progression to distant disease. As a rule, the delay in diagnosis measures months and years [2], and symptoms of airway obstruction are erroneously attributed to adult onset asthma [3]. The time point of diagnosis determines the prognosis of the disease, and unresectable tumors are associated with prolonged symptom duration [2]. The physician is faced with a challenge of finding an uncommon diagnosis for common symptoms. Population-based studies suggest that few patients undergo surgical resection, the treatment affording the best long-term prognosis [3-5]. Finding resection rates for tracheal tumors as low as 10% in Denmark, Licht and associates assumed a lack of knowledge as the cause and accused physicians of therapeutic nihilism [3]. A Multidisciplinary audit of 50 cases of tracheal cancer in the Netherlands found that a majority of patients with potentially resectable disease was treated with other modalities than curative surgery [6]. We review the available literature on the epidemiology, diagnosis and management of this group of tumors to summarize the available knowledge about these uncommon tumors.

Materials and Methods

We searched PubMed using the MeSH-term 'Tracheal Neoplasms' with subheadings, including only English language publications of primary tracheal malignancies in humans between January 1960 and July 2009. Of the 1469 search results, 66 articles reporting on series of ten or more patients with true primary tracheal cancer were included in this review. More than 40 additional references were acquired from the bibliographies of the selected articles.

Epidemiology

Ninety percent of all tracheal tumors in adults are malignant [7], in contrast to approximately 30% in children [8]. The incidence of primary tracheal cancer is approximately 0.1 in every 100.000 persons per year [4,9]. These tumors make up approximately 0.2% of all tumors of the respiratory tract and account for 0.02 – 0.04% of all registered malignancies [3,9,10]. Cancers of the larynx and bronchi occur approximately 40 and 400 times more frequent than cancer of the trachea, respectively.

Squamous cell tracheal carcinoma usually develops in the sixth or seventh decade and is more common in men and smokers [9]. In contrast, adenoid cystic carcinoma tends to occur in younger patients, is not smoking-related and equally distributed among the sexes [11-13]. The relatively low incidence of squamous cell carcinoma of the trachea when compared with laryngeal and bronchial cancer is attributed to the

laminar airflow in the trachea [14], which might prevent the deposition of carcinogens in the tracheal mucosa.

Table 1. Histologic Types of Tracheal Cancer Found in Epidemiologic Studies

Author	Year	Period	Type*	Cases	Histology	%	n
Kurien [41]	1981	1957-1974	R	97	Squamous cell carcinoma	46.4%	45
					Adenoid cystic carcinoma	3.1%	3
					Small cell carcinoma	5.1%	5
					Adenocarcinoma	6.2%	6
					Other†	39.2%	38
Manninen [9]	1991	1967-1985	N	95	Squamous cell carcinoma	71.6%	68
					Adenoid cystic carcinoma	6.3%	6
					Small cell carcinoma	7.4%	7
					Adenocarcinoma	12.6%	12
					Other	2.1%	2
Gelder [1]	1993	20 years	P	321	Squamous cell carcinoma	52.4%	174
					Adenoid cystic carcinoma	10.6%	34
					Small cell carcinoma	5.0%	16
					Adenocarcinoma	4.0%	13
					Large cell carcinoma	5.9%	19
					Other‡	20.2%	65
Yang [104]	1997	1979-1994	S	67	Squamous cell carcinoma	52.2%	35
					Adenoid cystic carcinoma	7.5%	5
					Small cell carcinoma	6.0%	4
					Adenocarcinoma	14.9%	10
					Other	19.4%	13
Licht [3]	2001	1978-1995	N	109	Squamous cell carcinoma	63.3%	69
					Adenoid cystic carcinoma	7.3%	8
					Small cell carcinoma	7.3%	8
					Adenocarcinoma	10.1%	11
					Large cell carcinoma	1.8%	2
					Other	10.1%	11
Honings [4]	2007	1989-2002	N	308	Squamous cell carcinoma	52.9%	163
					Adenoid cystic carcinoma	7.1%	22
					Small cell carcinoma	11.0%	34
					Adenocarcinoma	6.2%	19
					Large cell carcinoma	7.5%	23
					Other	15.3%	47
Total				997	Squamous cell carcinoma	55.6%	554
					Adenoid cystic carcinoma	7.8%	78
					Small cell carcinoma	7.4%	74
					Adenocarcinoma	7.3%	73
					Large cell carcinoma	4.4%	44
					Other	17.5%	174

* N = national registration, S = single institution, P = nationwide postal survey, R = regional registration

† Study includes 25 cases with unknown histologic type

‡ Study includes 44 cases with unknown histologic type

Histology

The two most common tracheal carcinomas are squamous cell carcinoma and adenoid cystic carcinoma [2,15-19], occurring in 36 – 45% and 31 – 40% of tracheal tumors [17,20], respectively. Even a majority of the remaining tumor types is malignant [21], including non-squamous bronchogenic carcinoma, mucoepidermoid carcinoma, carcinoid tumors, sarcomas, melanomas and lymphomas. Benign tumors are found in 11 – 13% [17,20]. These data are derived from clinical studies, since population-based studies do not contain either pathologic or radiologic review and are therefore unreliable [6]. The high proportion of adenocarcinoma and small cell carcinoma, for example, in national studies suggests a contamination with lymph node metastases from lung and mediastinal tumors [22]. Where a radiologic review has been part of epidemiologic data, the low incidence of non-squamous bronchogenic carcinoma has been confirmed [6].
Squamous cell carcinoma makes up more than half of all carcinomas in population-based series [3,4,9] (Table 1), and yet their more rapid natural history and progression of disease leads to a lack of referral for curative therapy. In contrast, adenoid cystic carcinoma grows far more slowly but is amenable to surgical resection for a longer period of time [23]. Complete resection, however, is hard to achieve due to extensive submucosal growth [23]. Although prognosis is better than in squamous cell carcinoma, adenoid cystic carcinoma is known for its tendency to develop late local and distant recurrences, which can occur up to 30 years after treatment [24].

Presentation and Diagnostic Evaluation

Tracheal tumors are most commonly misdiagnosed as adult onset asthma. Symptoms usually include dyspnea (58%), cough (54%), hemoptysis (45%), wheeze (36%) and stridor (24%) [2]. These symptoms develop over months and years [2,25] and may be treated with inhaled medications or even oral steroids [26-28]. Airway obstruction is often advanced and life-threatening at the time of diagnosis [29]. Patients will develop symptoms like dyspnea on exertion, dyspnea in rest and stridor when the tracheal lumen is progressively obstructed. Stridor and dyspnea at rest will predominantly develop when the tumor is located at the cranial part of the trachea and the remaining surface of the lumen is severely compromised [29-32].

Continuous progression or new onset of adult asthma requires radiographic evaluation. Also, hemoptysis or hoarseness should alert the physician to the possibility of malignant upper airway pathology. Conventional chest roentgenograms can be used to exclude other forms of pathology, but are rarely diagnostic for tracheal neoplasms. According to studies by Manninen and co-workers and Honings and associates, chest X-ray identified a tracheal tumor in only 8 of 44 (18%) and in 14 of 50 (28%) patients with tracheal cancer, respectively [6,33].

Pulmonary function testing is an accessible and non-invasive tool that can easily be performed and may offer important clues for the diagnosis of tracheal tumors (Figure 1). The effect of anatomical lesions on maximal airflow depends on the site of obstruction, the type of lesion (variable or fixed) and the extent of anatomical obstruction. In patients with an extra-thoracic obstruction, the maximum inspiratory flow is decreased. A fixed obstruction will result in a decreased inspiratory and peak expiratory flow (PEF). Also, the maximum inspiratory flow at 50% of the forced vital capacity (MIF50) will be decreased and approximately equal to the maximal expiratory flow at 50% of the vital capacity (MEF50). This will therefore result in a MIF50/MEF50 ratio of approximately 1. In contrast, a variable extra-thoracic obstruction will result in a decreased MIF50 but a normal or decreased PEF, and consequently a reduced MIF50/MEF50 ratio of usually less than 1.
In patients with an intra-thoracic tracheal tumor located below the thoracic inlet, a fixed or variable obstruction airflow pattern as described above can be seen. Intra-thoracic airway obstruction is characterized by a decreased PEF, a normal or decreased MIF50 and consequently a MIF50/MEF50 ratio of 1 or more [34]. However, when central airway pathology is suspected, endoscopic inspection of the tracheobronchial tree is warranted, even in the absence of a spirometric pattern suspect for central airway obstruction.

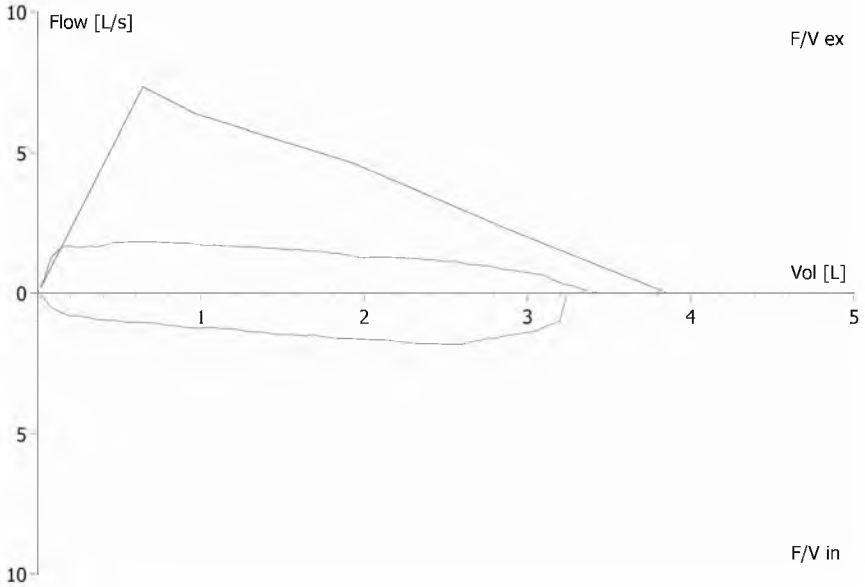


Figure 1. This flow volume curve shows severe inspiratory and expiratory airway obstruction caused by an intratracheal tumor. Straight line indicates predicted expiratory curve

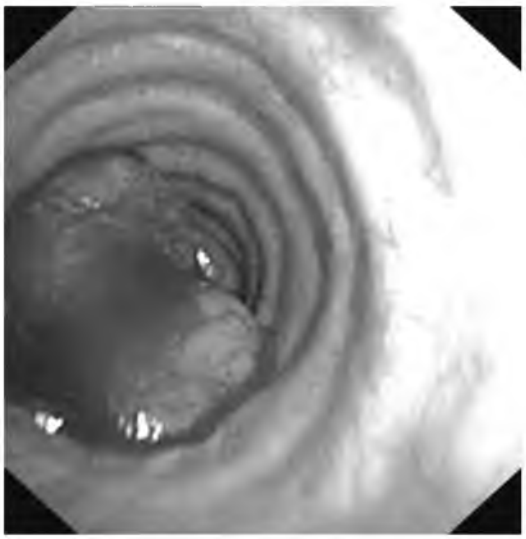
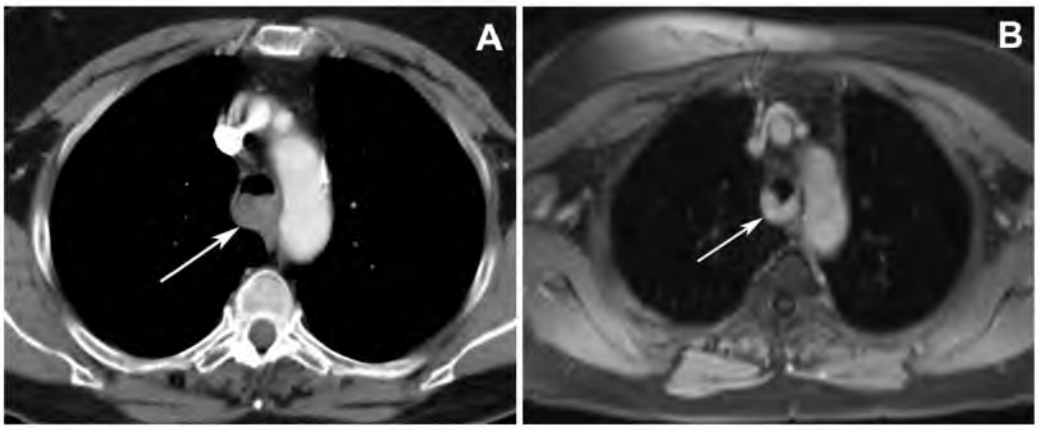


Figure 2. This endoscopic view shows high grade narrowing of the trachea caused by an adenoid cystic carcinoma at the time of diagnosis. Endoscopic debridement may precede definitive treatment to prevent acute airway obstruction

The most useful test in diagnosing tracheal cancer is bronchoscopy (see Figure 2). Bronchoscopy provides an accurate evaluation of the nature and the extent of the tumor. Location and length can be related to anatomic landmarks such as the carina and the cricoid cartilage and tumor dimensions can be related to the airway diameter. Furthermore, a tumor biopsy can be taken for pathologic evaluation. Flexible tracheobronchoscopy however can provoke cough, edema and bleeding of the airway, which in turn could aggravate the obstruction of the airway. In patients with acute respiratory distress, the use of rigid bronchoscopy is advised.

Together with tracheobronchoscopy, chest and neck computed tomography (CT) scans form the mainstays for diagnosing and staging of primary tracheal tumors [35]. CT scans are helpful to assess the depth of invasion, possible involvement of adjacent structures and to search for lymphogenic and distant metastasis or synchronous primary tumors (Figure 3A). Diagnostic recommendations based on this study are summarized in Table 2. Currently, novel imaging techniques for the evaluation of the upper airway are under study, including three-dimensional virtual tracheoscopy, super-high resolution computed tomography scanning and endoscopic ultrasound [36]. Esophagoscopy may provide information about esophageal invasion.



Figures 3A and 3B. Axial imaging of the trachea by either CT scan (panel A) or MRI (panel B, T1 weighted) demonstrate degree of obstruction and show here the absence of extratracheal invasion. Note that neither study may rule out esophageal invasion. Arrow indicates tumor arising from membranous portion

Staging of Tracheal Cancer

At this moment, there is no TNM staging system available for malignancies of the trachea [37]. The definition of lymph node involvement used in the TNM-classification for bronchial carcinoma cannot be applied to tracheal carcinomas [38,39].
Efforts to create a staging system for tracheal cancer are impeded by the low incidence of this tumor. Bhattacharyya suggested a tumor and lymph node dependent staging system in 2004 [40]. In 23 patients with mixed histology (squamous cell carcinoma; 11, adenoid cystic carcinoma; 9, other; 3) the system as proposed by Bhattacharyya proved a significant predictor of survival, although groups were small and both surgery and radiotherapy were used in unknown proportion in each stage [19]. Recently, a new staging system was proposed by Macchiarini [41]. This system is based upon a TNM classification in combination with tumor localization in the trachea (upper, middle and lower). The suitability of both systems and their therapeutic and prognostic implications are not yet clarified and should be subject of further investigation.

Table 2. Diagnostic Recommendations for Malignant Tracheal Tumors

Chest X-ray and/or chest CT for:
Dyspnea, stridor or wheezing unresponsive to bronchodilators
Upper airway obstruction at spirometry, unresponsive to bronchodilators
New cough for more than three weeks
Bronchoscopy:
No abnormalities, explanatory for symptoms
Tracheal mass, compression or deviation
Chest CT and bronchoscopy:
Hemoptysis
Persistent hoarseness

CT = computed tomography

Apart from staging, assessment of local resectability is essential in the work-up of patients. Based on the experience of a center for airway surgery with selected referral, Gaissert and colleagues stated that locoregional, and not distant, disease determines resectability in most patients [2]. In the presence of a localized tracheal carcinoma, every patient should undergo an evaluation to determine resectability and the histologic diagnosis consisting of radiographic and bronchoscopic examination with computed tomography of the neck and chest. Magnetic resonance imaging can also be used (Figure 3B), but provides no advantage over computed tomography. When clinically indicated, workup can be expanded with various investigative modalities. Positron emission tomography (PET) scanning can be used to assess local lymph node involvement and distant metastases, endo-esophageal ultrasound or esophagoscopy can be performed to investigate ingrowth in the esophagus, computed tomography or ultrasound of the abdomen, bone scintigraphy

and magnetic resonance imaging of the cerebrum can be used to detect distant metastases. The recommended steps in the workup of biopsy proven tracheal carcinoma (after bronchoscopy) are shown in Table 3.

Table 3. Workup for Biopsy Proven Primary Tracheal Cancer

When acute intervention is necessary to maintain airway
Salvage endoscopic debulking
Do not perform procedures which prohibit surgical resection (such as stents or tracheostomy)
Always perform
CT of the neck
CT of the chest
When tracheoscopy or neck CT shows possible invasion of esophagus
Esophagoscopy and/or endo-esophageal ultrasound
When clinically indicated
PET scan
CT or ultrasound of the abdomen
Bone scintigraphy
CT or MRI of the cerebrum

CT = computed tomography, PET = positron emission tomography, MRI = magnetic resonance imaging

Treatment

In the management of primary tracheal cancer, it is necessary to be familiar with the full range of available treatment modalities. Only when the multidisciplinary team has sufficient knowledge and experience with these techniques can a good decision be made on the appropriate management in a specific patient.
Since resection is the treatment with the greatest potential to change the natural history of disease, a focus on selecting candidates for resection is important. Other forms of treatment serve as adjuvant after or palliative treatment in place of surgical resection [2,42].

Management of Acute Airway Obstruction
Acute airway obstruction with imminent suffocation requires urgent relief of symptoms using rigid bronchoscopy [29]. During this procedure it is possible to improve airway patency by endotracheal tumor debulking. Temporary enlargement of the airway provides time to complete the assessment of resectability and prepare the patient for elective surgery. We advise against airway stenting, tracheostomy and pre-operative radiotherapy in the acute setting, as these procedures may impair the results of definitive surgical treatment [43].

Surgery

Airway obstruction caused by tracheal cancer is immediately relieved with surgical resection of the involved tracheal segment. This approach, with or without post-operative radiotherapy, offers long-term survival in many and cure of disease in some patients [7]. Webb and associates advocate standard application of adjuvant radiotherapy in all patients operated for tracheal cancer [44].

Tracheal resection is a well established technique with predictable success. Salassa and colleagues described the vascular anatomy of the trachea and Grillo and Pearson and their co-workers developed surgical mobilization techniques by which up to 50% of the tracheal length may be removed with subsequent primary reconstruction, without compromising anastomotic healing [45-53]. This technique was further developed for resection and reconstruction of the carina [54,55]. Even in some proximally located tracheal tumors with extension into the subglottic larynx, radical resection can be achieved by cricotracheal resection and primary reconstruction, without jeopardizing the function of voice [56]. Concurrently with these developments and the growing experience in tracheal surgery, operative mortality has declined at centers of experience to approximately 3% in the past decade [2].

Surgery is contra-indicated when complete tumor resection would result in excessive tension at the anastomosis, often when tumor length exceeds 50% of the trachea, when vital organs (aorta, heart) are involved by tumor, the mediastinum has received high-dose irradiation therapy, or massive lymph node invasion is present [2,7,57]. The latter condition precludes radical surgery, because the lateral arterial blood supply to the trachea would be seriously compromised after radical lymphadenectomy [7]. Because adenoid cystic carcinomas usually progress slowly, even in the presence of distant metastasis, surgical resection may be beneficial to the patient [58]. This is in contrast to squamous cell carcinoma, where distant metastases are more common.

Through the decades, various techniques have been evaluated to replace trachea with foreign materials, nonviable tissue, autogeneous tissue and allo- and xenotransplantation [59]. Recently, Wurtz and associates reported the successful use of aortic allografts enforced with silicone stents in two patients, who had good respiratory function after 18 months of follow-up [60]. An international group with Macchiarini and Birchall reported a case in which the left mainstem bronchus was replaced with a de-cellularized and de-antigenized donor tracheal transplant colonized by the recipients epithelial cells and chondrogenic mesenchymal cells [61]. Enforced free cutaneous flaps have also been used with success [59,62-64]. Long-term outcome of these techniques is still unknown. Further research and refinement of these techniques are required. Nonetheless, they might hold some promise for the future of tracheal surgery.

Radiotherapy

Radiotherapy in tracheal carcinoma is applied either as adjuvant therapy after resection or as primary therapy in unresectable or inoperable patients. Postoperative radiotherapy can be applied to improve survival by reducing the chance of local

recurrence [26,65]. The results of primary radiotherapy are inferior compared to those of surgery [1,5,20,65-71].

Because of the rarity of the disease, many studies included patients treated several decades ago, even in the 1950's and 60's. At that time radiotherapy equipment and radiation techniques had their limitations and often suboptimal doses and fractionation schedules were used. Also, several studies combine tumors of different histology. Adenoid cystic carcinomas are generally considered to be less radiosensitive than squamous cell carcinomas.

Some more recent studies indicate that better results can be obtained with higher radiation doses [68,71-73]. Bittner and associates recently reported a 5-year survival of 89.4% in 19 patients with unresectable adenoid cystic carcinoma treated with fast neutron radiotherapy in combination with endobronchial brachytherapy in 6, although the 5-year disease free survival was only 28% and 6 of 12 failures occurred locally, all within the field of treatment [74]. Although the general outlook remains poor for patients with advanced and unresectable tumors, 5-year survival rates of 25-30% can be obtained with adequately dosed radiotherapy indicating that there is a subgroup of patients that can be cured [72,73]. Using higher doses, the risk of complications is increased. Modern techniques such as conformal radiotherapy and intensity-modulated radiotherapy (IMRT) may incrementally reduce the risk of higher doses by lowering the exposed tissue volume. When external beam radiotherapy is used in a curative setting, a dose of at least 60 Gy and, if possible, up to 70 Gy in daily fractions of 1.8 – 2.0 Gy is recommended [41,69,71,72]. A dose of 60 Gy is recommended for microscopic residual disease in an adjuvant situation [41]. Adequate dose delivery requires at least CT-based planning and three dimensional conformal treatment techniques with position verification. Another approach is to deliver the boost dose through intraluminal brachytherapy [71,73,75-79]. To this end, the use of a special applicator which secures central positioning of the source within the tracheal lumen is mandatory. Central positioning of the brachytherapy catheter in the lumen enables a homogeneous dose distribution and prevents high contact doses delivered to the tracheal mucosa.

Thus, primary radiotherapy should be considered as a curative option for patients with advanced unresectable disease in good general condition and for patients with resectable disease but not sufficiently fit for surgery. In other cases radiotherapy can provide palliation with good symptomatic relief. Amelioration of hemoptysis and obstruction was reported in three-quarters of the patients and reduction of dyspnea and cough in approximately half [67].

Endotracheal Treatment

Various endotracheal techniques are available which all aim to dilate the airway obstruction or debulk tumor mass in the trachea in order to provide a patent airway [29]. These procedures are performed during rigid bronchoscopy under general anesthesia. With the rigid tracheobronchoscope it is possible to maintain ventilation during the procedures. Endotracheal techniques can be used in two clinical settings: acute relief of airway obstruction, which might be prior to definitive surgical

treatment, and palliation in patients with unresectable disease. In both settings, endoscopic debridement is a minimally invasive procedure, which immediately relieves symptoms [31]. Tumor mass may be removed with mechanical core out [80,81], electrocoagulation, neodymium-doped yttrium aluminum garnet (Nd:YAG) laser [82-87], carbon dioxide laser [88-90] or argon beam [91,92] coagulation, cryotherapy [93-95] or photodynamic therapy [96-98].
As stated before, long term airway stenting should be prevented as much as possible in patients who might be candidate for airway resection [32]. However, when patients suffer from unresectable disease, airway stenting, in some patients preceded by tumor debulking, may effectively secure the airway and improve quality of life even in the long term [32,99-103].

Systemic Therapy
In the absence of prospective trials, the value of systemic chemotherapy in patients with unresectable tracheal cancer or as adjuvant therapy in combination with surgery or radiotherapy remains uncertain.

Outcome and Prognosis

Prognosis of patients with tracheal cancer is dismal. Population-based studies from Europe have shown that the 5- and 10-year survival rates of all types of tracheal carcinoma are 5-15% and 6-7%, respectively [3,4,42]. In these studies, it is emphasized that patients treated with surgical resection have better prognosis, the 5- and 10-year survival rates being 50% and 35-50%, respectively [3,4]. Several reports from surgical clinics have shown similar outcomes: airway resection yields improved survival [20]. In a Russian study by Perelman and colleagues [104], resection was performed for malignant tracheal tumors in 120 patients, of which 55% had adenoid cystic carcinoma. 5- and 10-year survival rates were 36% and 27%, respectively [104]. In a French multicentre study by Regnard and associates, the 5-year survival rate after surgery for adenoid cystic carcinoma was 73% (n=63) and 47% for tracheal carcinomas other than adenoid cystic carcinoma (n=94) [17]. In 29 patients with adenoid cystic carcinoma reported by Maziak and colleagues, 5-year survival was 79%, although three operative deaths were excluded from survival analysis [24]. A Japanese study by Hazama and associates reported a 5-year survival rate of 53% in nine cases of resected squamous cell carcinoma and even 100% in seven cases of resected adenoid cystic carcinoma [15]. Gaissert and colleagues found that the 5-year survival rates in resected patients were 39% in squamous cell carcinoma (n=90) and 52% in adenoid cystic carcinoma (n=101) [2]. In 2006, the same group showed that, also in patients with uncommon primary tracheal neoplasms, such as carcinoid and sarcoma, airway resection leads to long-term survival and is superior to local endoscopic tumor destruction [21]. In a recently published Chinese study, the reported 5-year survival was 40% in 35 cases of ACC, of which 28 underwent resection and 7 only received radiotherapy [105]. These data are summarized in Table 4.

Table 4. Results after Segmental Tracheal Resection for Primary Tracheal Cancer

					Survival (%)	
Author	Year	Country	Period	Cases	5-year	10-year
Squamous cell carcinoma						
Gaissert [2]	2004	USA	1962-2002	90	39	18
Hazama [15]	2003	Japan	1979-2000	9	53	53
Regnard [17]	1996	France	1970-1993	65	73	51
Adenoid cystic carcinoma						
Zhengjaiang [103] *	2008	China	1981-2002	35	40	
Honings [4]	2007	Netherlands	1989-2002	18	77	41
Gaissert [2]	2004	USA	1962-2002	101	52	29
Hazama [15]	2003	Japan	1979-2000	7	100	100
Maziak [23]	1996	Canada	1963-1995	32	39	51
Various histologic types						
Honings [4] †	2007	Netherlands	1989-2002	34	51	35
Perelman [102] ‡	1996	Russia	1963-1995	120	36	27

* Of 35 cases, 28 underwent resection and 7 received primary radiotherapy
† Histologic types: 53% squamous cell carcinoma, 32% adenoid cystic carcinoma, 15% other
‡ Histologic types: 55% adenoid cystic carcinoma, 18% squamous cell carcinoma, 17% carcinoid, 10% other

The most important prognostic factors in primary tracheal carcinoma are histology and treatment: adenoid cystic carcinoma and mucoepidermoid carcinoma have a better prognosis than other histologic types [106-108] and survival in resected patients is better than in non-resected patients, particularly when resection is histologicly complete [3-5]. This is not only the case in small and locally confined tumors. In patients even with advanced tumors, surgery yields the best survival and chances of cure of disease. In adenoid cystic carcinoma, because of its slowly progressing character and adjuvant radiotherapy, tension-free anastomosis is more important than tumor free resection margins [17,109].

Another factor that needs to be addressed is lymph node involvement. The role of positive lymph nodes in tracheal cancer is still unclear. Macchiarini suggested a staging system based upon tumor size, infiltration depth, involved organs, lymph node spread and presence of distant metastasis. The correlation with survival yet remains to be investigated [41]. Bhattacharyya advocated a tumor and node-based staging system, where stage IV would include both T4 and patients with any T-status and one or more positive lymph nodes [40]. After correction for histologic type, survival in stage III (T3N0) and IV was identical. Further, each stage comprised a heterogeneous group including patients treated with surgery with or without radiotherapy, radiotherapy alone and patients with unknown treatment. Regnard and associates did not find a decrease in survival in patients with positive lymph nodes [17]. This finding was iterated by Gaissert and colleagues, who commented that this might be due to the small sample size [2].

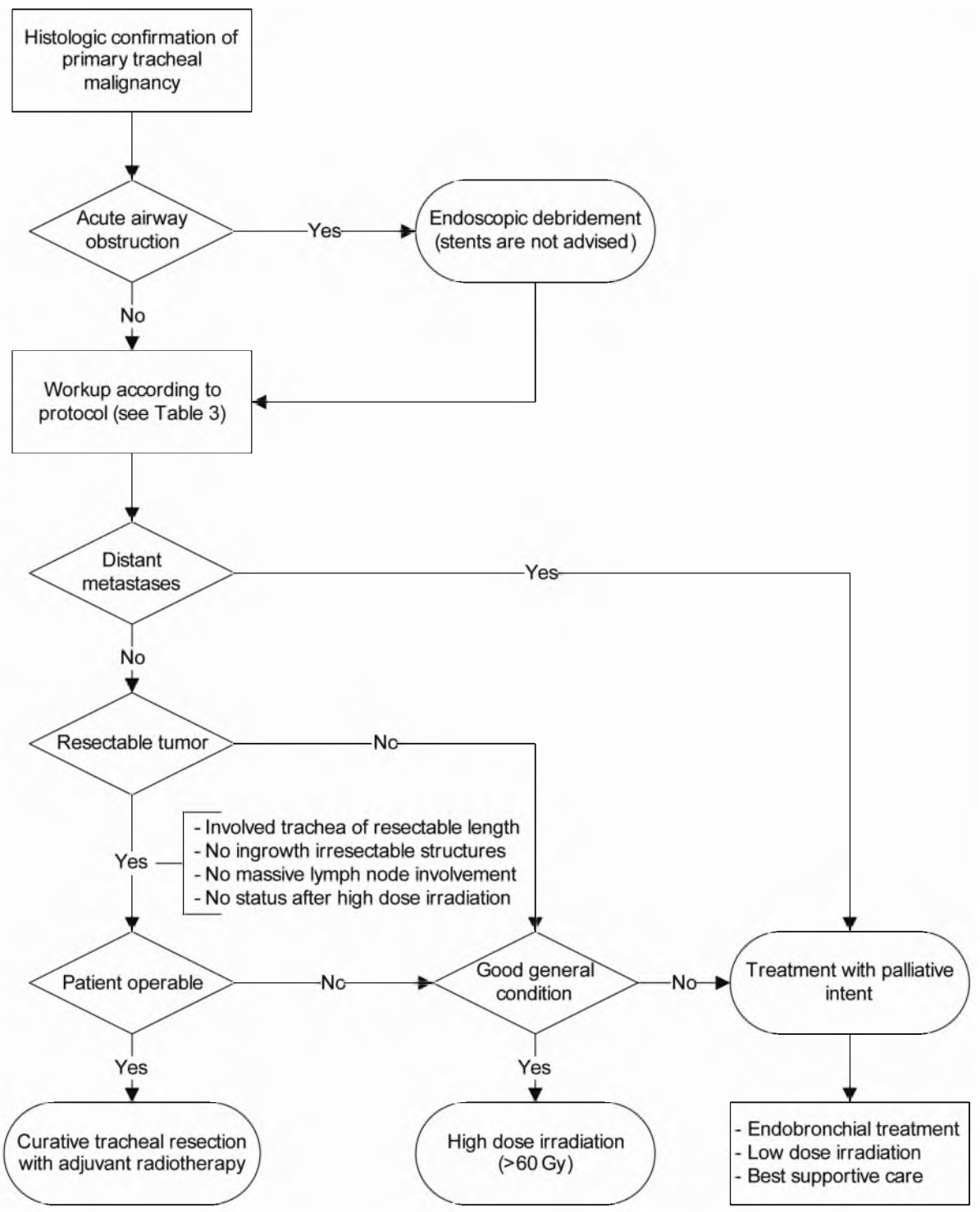


Figure 4. Proposed treatment algorithm for primary tracheal malignancy

The influence of nodal metastases in tracheal cancer needs to be elucidated. In view of this and in the absence of retrospective or prospective proof we are not able to recommend any staging system.
Most important in improving the survival of patients with primary tracheal malignancies seems to be selecting the patients who are amenable for definitive surgery. The treatment algorithm depicted in Figure 4 is primarily focused on this aspect and may contribute to a situation in which more patients with tracheal cancer are treated with curative intent. The judgment whether distant metastasis form a contra-indication should be precisely made for each individual patient, especially in the case of adenoid cystic carcinoma [58]. Such considerations and the delivery of definitive surgical care can best be done in tertiary centers specialized in tracheal surgery. In Europe, only 10% of patients with tracheal cancer is treated with airway resection [1,3-5,42], though in principle this is feasible in more than half of all patients [15,43]. This statement is further reinforced by a recent audit in the Netherlands [6]. By implementing a centralized care system, more patients might be treated with airway resection. Also, morbidity and mortality from airway surgery are lower in the hands of experienced airway surgeons [2,17,58].

Conclusion

Primary malignancies of the trachea are rare and diagnosis is often delayed due to its aspecific symptoms. Several studies have suggested a lack of knowledge and expertise in clinicians facing patients with tracheal tumors, ultimately leading to a relative undertreatment of this challenging disease. Surgical resection, in the vast majority followed by primary reconstruction and postoperative radiotherapy in case of microscopic residual disease, is the best curative treatment modality available at present. Currently, no validated staging system exists, for which future prospective research is warranted. However, we feel that most important in the workup of patients with tracheal cancer is selecting patients who might be amenable for surgical resection, which is expected be the case in more than 50% of patients. Radiotherapy should only be used as adjuvant therapy after airway resection and in patients with unresectable disease or in patients who are inoperable. Centralizing the care for patients with tracheal malignancies could lead to an increase in long-term survival and a decrease in operative morbidity and mortality.

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CHAPTER THREE

3.1 – Pathologic Characteristics of Resected Squamous Cell Carcinoma of the Trachea: Prognostic Factors Based on an Analysis of 59 Cases

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ABSTRACT

Background: While squamous cell carcinoma (SCC) is the most common tracheal malignancy, few reports describe the pathologic considerations that may guide intraoperative decisions and prognostic assessment.

Methods: We reviewed 59 tracheal SCC treated between 1985 and 2008 by segmental resection of the trachea, including resection of the carina in 24% and inferior larynx in 14%. We classified these tumors by grading histologic differentiation and microscopic features used in SCC of other sites.

Results: Of 59 tumors, 24% (14/59) were well differentiated, 49% (29/59) were moderately differentiated, and 27% (16/59) were poorly differentiated. Unfavorable prognostic factors were tumor extension into the thyroid gland (all of 5 so afflicted patients died of tumor progression within 3 years) and lymphatic invasion (mean survival 4.6 versus 7.6 years). Keratinization, dyskeratosis, acantholysis, necrosis, and tumor thickness, did not predict prognosis.

Conclusion: As surgical resection is the only curative treatment, the surgeon should establish clean lines of resection, using as appropriate intraoperative frozen section. The pathologist can provide additional important prognostic information, including tumor differentiation and extent, invasion of surgical margins, and extension into the thyroid.

Introduction

Although squamous cell carcinoma (SCC) accounts for more than half of all tracheal tumors [1], the pathologic features in resection specimens and the impact of these features on survival have only been described in small series [2]. At least two staging systems have been proposed for tracheal malignancies; one, a cross-sectional analysis of a national cancer database by Bhattacharyya, is based on retrospective TNM documentation correlated with survival statistics in 41 squamous cell carcinomas, 19 adenoid cystic carcinomas and 32 tumors of other histology [3], although a TNM staging system validated by clinical and pathologic evidence for this disease does not exist. The other, by Macchiarini, is a non-validated TNM-classification [4]. Both classifications are intended to be applied to all histologic types of tracheal cancer.

We describe specific pathologic features of primary tracheal SCC in a large series of surgical specimens from a single institution to identify prognostic predictors of survival.

Materials and Methods

A retrospective analysis was conducted of consecutive patients who underwent resection for primary SCC of the trachea from 1985 to 2008 at Massachusetts General Hospital (MGH) and for whom pathology slides or blocks were available. All except 4 patients were included in a previous report describing the surgical results [5]. We included one patient in whom a second resection at MGH completed tumor excision after a first resection elsewhere. One patient underwent 3 resections, but only the first, for tumor resection, was included in this study. Pathology reports, operative reports, and hospital charts were reviewed to exclude laryngeal cancer and tumors of the lung that extended to the carina. The MGH institutional review board approved the most recent protocol (No. 2008-P-000113) in January 2008.

Types of Resection

The surgical technique has been detailed previously [6]. For standard tracheal resection, a sleeve of trachea was removed with end-to-end reconstruction, resulting in 2 airway margins and a radial soft tissue margin. When tracheal resection was combined with laryngectomy, cervical or mediastinal end-tracheostomy was required. For laryngotracheal resection, the tumor was removed with a portion of infraglottic larynx while preserving at least one recurrent laryngeal nerve not involved with tumor. Reconstruction was achieved by shaping the remaining trachea to conform to the laryngeal defect. Carinal resection was performed with or without concomitant lung resection resulting in either 2 or 3 airway margins, respectively. Systematic lymph node dissection is assumed to interfere with the tracheal blood supply and was therefore not performed. Regional lymph nodes were often not included in the specimen if not grossly enlarged. Absence of tumor at the airway

margins was confirmed by frozen section unless the limits of resection had been reached and no additional trachea could be removed.

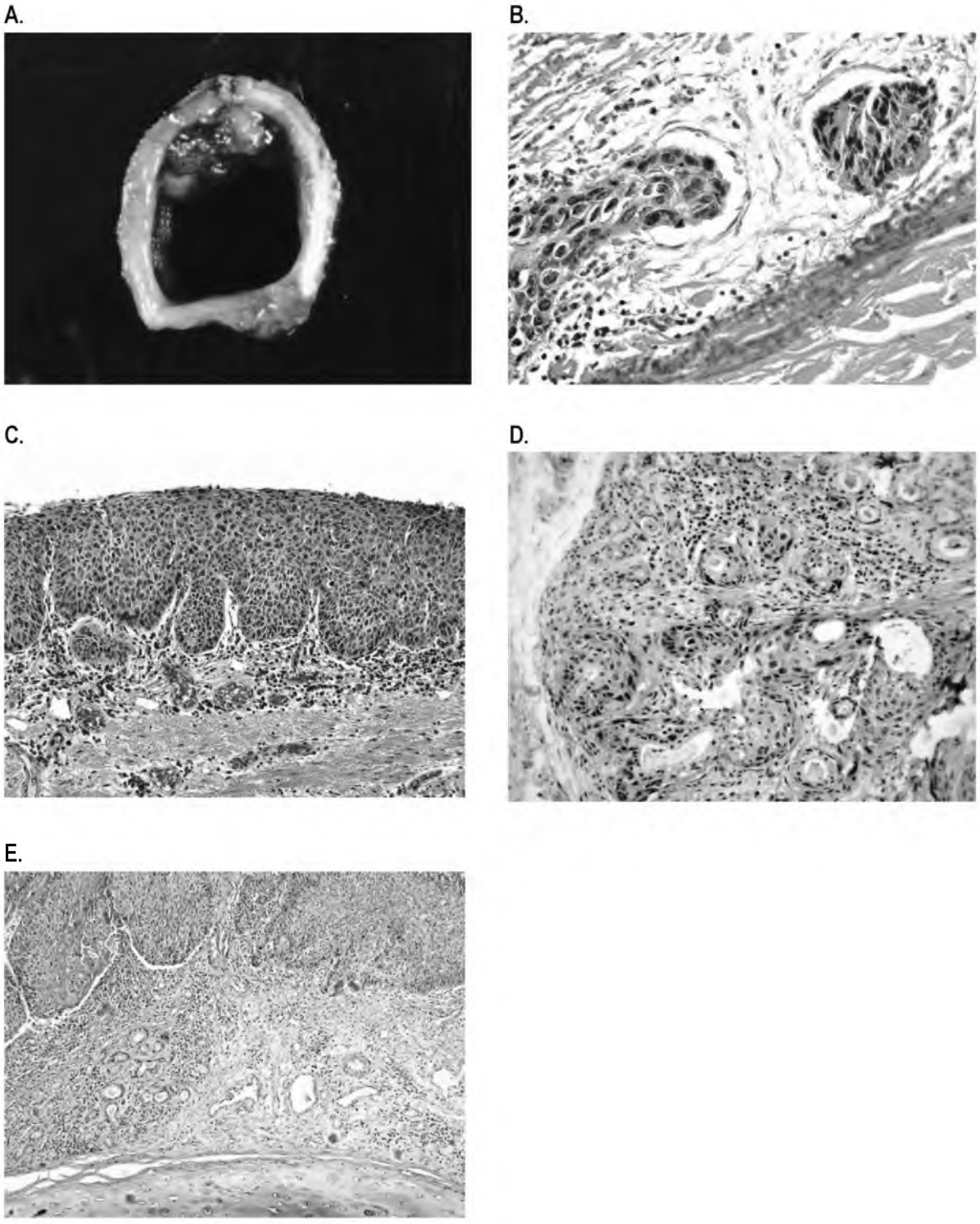


Figure 1. A. Cross section of trachea with exophitic tumor attached to anterior wall; B. Lymphatic invasion in peritracheal adventitia; C. Squamous cell carcinoma in situ, with full thickness replacement of epithelium by cells with hyperchromatic nuclei and lack of surface maturation; D. Cancerization of mucus ducts and glands by malignant squamous cells but no invasion beyond basement membrane; E. Squamous cell carcinoma invading from surface epithelium into lamina propria and eliciting inflammation and fibrosis but not as far as tracheal cartilage (bottom)

Pathologic Review and Tumor Data

In all reviewed cases, photographs of the resected specimen (Figure 1A) and slides stained with hematoxylin and eosin were retrieved. Slides were recut from stored blocks if necessary. Pathologic review of two or more slides per case was done in each case by a senior pulmonary pathologist (E.J.M.), on average 4 to 6 slides of the tumor itself and additional slides of resection margins and lymph nodes. The following histologic features were scored: degree of differentiation based on degree and extent of nuclear pleomorphism, using the criteria for well, moderately, or poorly differentiated subtypes in the AFIP Atlas of Tumor Pathology [7]; tumor thickness, defined as the distance from the luminal tumor surface to the farthest extent of invasion; keratinization; necrosis; dyskeratosis; acantholysis; and lymphatic invasion (Figure 1B). Since no TNM-based staging system currently exists for tracheal carcinoma, depth of tumor invasion into the tracheal wall was scored according to a system devised for the study as shown in Figure 2, with both squamous cell carcinoma in situ (Figure 1C) and invasion of carcinoma into tracheal mucus glands and ducts (so-called cancerization, Figure 1D) considered level 0 and superficially invasive (Figure 1E) as grade 1.

Further, operative and pathology reports were reviewed for length of resection in the long axis of the airway and the presence of tumor metastasis in lymph nodes. Since lymph node excision in tracheal resection occurs merely sporadic, we combined cases with positive lymph node biopsy and cases with lymphatic invasion on histologic examination, in order to provide a meaningful, albeit restricted analysis.

Adjuvant Radiotherapy

Postoperative radiotherapy was usually recommended at a dose of 54 Gy 6 to 8 weeks after resection and often administered outside Massachusetts General Hospital.

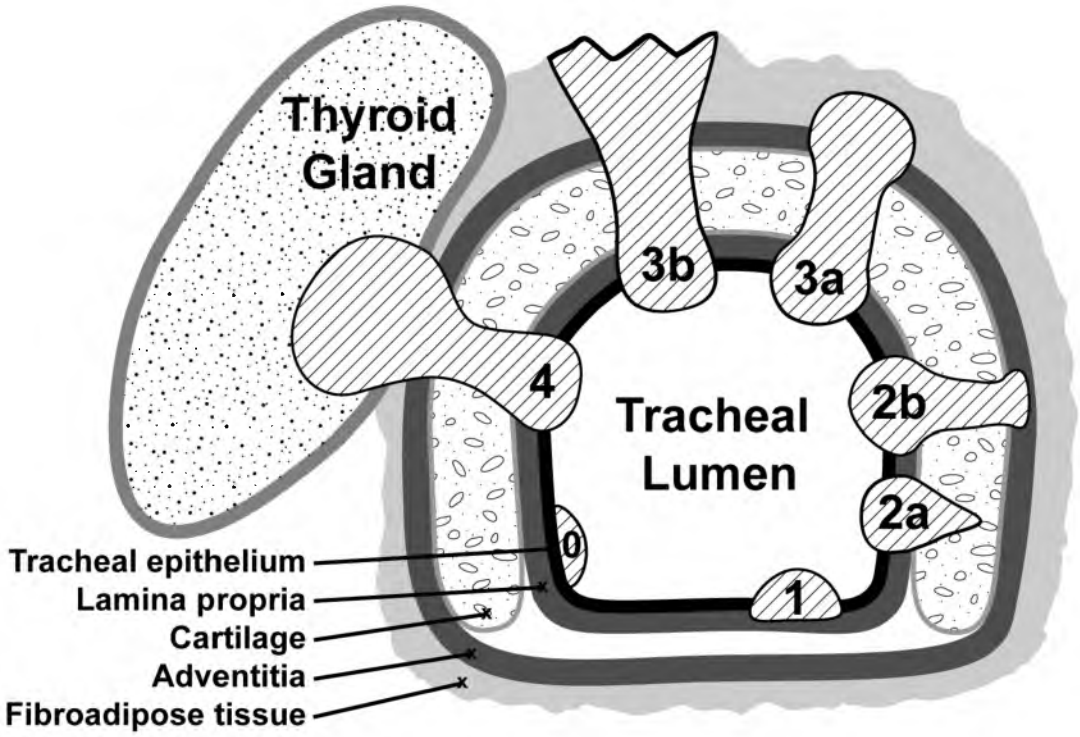
Follow-Up

Patients and the MGH cancer registry were contacted for follow-up information. The Social Security Death Index was searched. Patients were determined to have died if name, date of birth, and social security number matched. The survival period began on the day of operation and was concluded by death.

Statistical Analysis

Overall survival after airway resection was calculated using the Kaplan–Meier procedure with the log rank test implemented in the SPSS 14.0 statistical software program (SPSS Inc, Chicago, IL), in contrast to the earlier report that used an actuarial method [5]. Categorical variables were compared with the Chi-Square test and covariate analysis was done with Pearson's bivariate analysis.

Figure 2. Depth of invasion in tracheal squamous cell carcinoma ranked by levels. *Tumor invaded between cartilage plates and not through the cartilage*



Level	Definition
0	Carcinoma in situ
1	Infiltrating lamina propia
2a	Abutting or extending between cartilage
2b	Invading beyond cartilage
3a	Invading peritracheal fibroadipose tissue
3b	Abutting soft tissue resection margin
4	Invading into thyroid gland

Results

Since 1985, 75 patients have undergone surgical resection for tracheal SCC at Massachusetts General Hospital. There were no operative deaths. Slides or blocks were retrieved in 64 cases, of which 5 were excluded: there was no viable tumor after radiotherapy in 3 patients, a cutaneous SCC occurred at a tracheostomy site in 1, and two separate SCC were present in 1 other patient, of which only one was resected. Thus, the study included 59 cases.

Overall Characteristics

There were 44 men (75%) and 15 women (25%) with a mean age of 61.9 years (range 29 to 79 years). Prior locoregional or pre-operative radiotherapy was administered in 24% (14/59). Resection involved trachea only in 63% (37/59), trachea and carina in 24% (14/59) and trachea and larynx in 14% (8/59) of cases. Mean length of resected airway was 3.2 cm (range 1 to 6 cm). Pathologic characteristics are listed in Table 1. Postoperative radiation was documented in 42.4% of patients (25/59). We know of no patient who received postoperative chemotherapy.

Follow-up and Overall Survival

Mean follow-up in 59 cases was 5.5 years (range 1 month to 18.3 years). Survival information was complete in 90% of patients (53/59). Mean survival was 6.5 years and the 5- and 10-year survivals were 46% and 27%, respectively. Table 1 shows the survival calculated for each subgroup.

Differentiation

A majority of tumors had moderate differentiation, while close to half were equally distributed between well and poorly differentiated. Survival was longer in well differentiated tumors, though this difference was not significant (Figure 3A). Survival in well differentiated carcinomas was 8.8 years versus 5.8 years in the group of moderately and poorly differentiated carcinomas combined ($P = 0.117$).

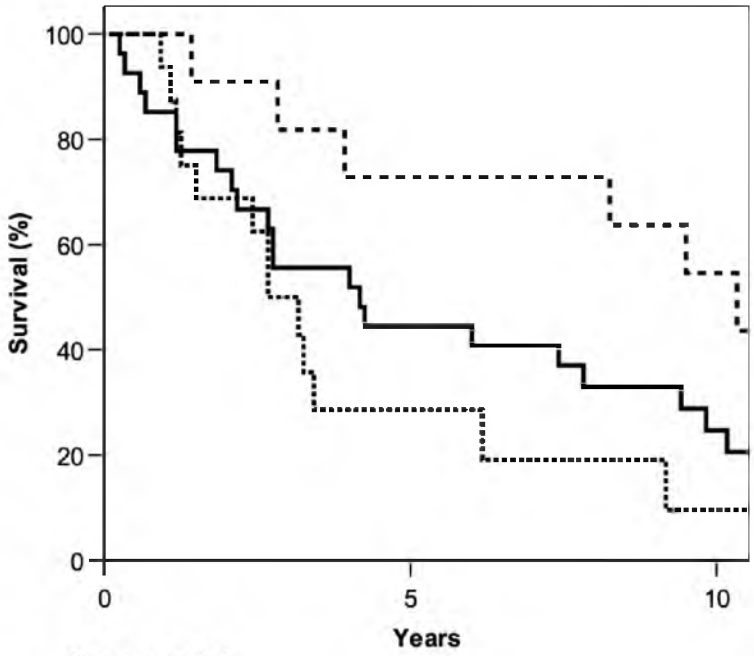
Keratinization, Necrosis, Dyskeratosis and Acantholysis

Two thirds of tumors (39/59) showed keratinization. Focal or extensive necrosis was present in 48% (28/59) and 20% (12/59), respectively. Necrosis was present significantly more frequently in moderately and poorly differentiated tumors (82%, 37/45) compared to well differentiated tumors (21%, 3/14; $P < 0.001$). Dyskeratosis was seen in 59% and acantholysis in 27%.

Survival was not significantly correlated with the presence or absence of keratinization, necrosis, dyskeratosis or acantholysis.

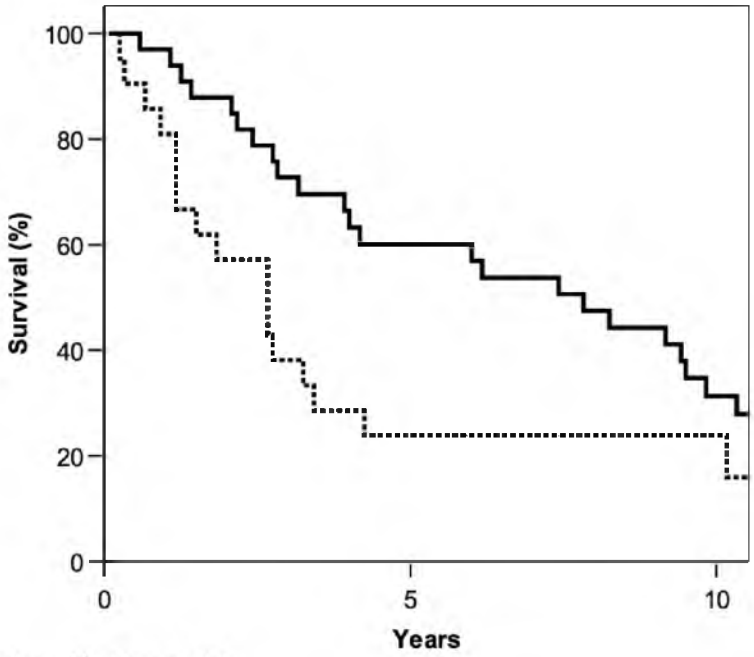
Table 1. Survival According to Pathologic Subgroups

Pathologic subgroup	No.	No. (%)	Mean survival (years)	*P*-value	Survival (%) 5-year	Survival (%) 10-year
Tumor differentiation						
Well differentiated	14	23.7	8.8		73	55
Moderately differentiated	29	49.2	6.3	0.164	44	25
Poorly differentiated	16	27.1	4.5		29	10
Keratinization						
Yes	39	66.1	6.5	0.719	50	28
No	20	33.9	6.6		39	26
Necrosis						
Extensive	12	20.3	7.2		46	27
Focal	28	47.5	6.1	0.726	45	26
No	19	32.2	6.2		47	30
Dyskeratosis						
Yes	35	59.3	6.7	0.942	51	34
No	24	40.7	6.3		39	20
Acantholysis						
Yes	16	27.1	5.6	0.307	47	31
No	43	72.9	6.9		46	26
Lymphatic invasion						
Yes	22	37.3	4.6	0.049	24	24
No	37	62.7	7.6		60	31
Depth of invasion						
Level 0	2	3.4	n.a.		100	100
Level 1	5	8.5	7.6		75	25
Level 2a	14	23.7	6.0		50	25
Level 2b	11	18.6	7.1	0.001	50	38
Level 3a	16	27.1	7.7		53	31
Level 3b	6	10.2	2.1			
Level 4	5	8.5	1.4		0	
Tumor thickness						
0.1 - 1.0 cm	29	49.2	6.8		48	32
1.1 - 2.0 cm	21	35.6	6.8	0.650	56	26
> 2.0 cm	9	15.3	4.1		13	13
Overall	59	100.0	6.5		46	27



Differentiation	Number at risk		
Well	14	8	5
Moderate	29	12	6
Poor	16	4	1

Figure 3A. Overall survival according to tumor differentiation



Lymphatic invasion	Number at risk		
Yes	22	5	3
No	37	19	9

Figure 3B. Overall survival according to lymphatic invasion

Lymphatic Invasion

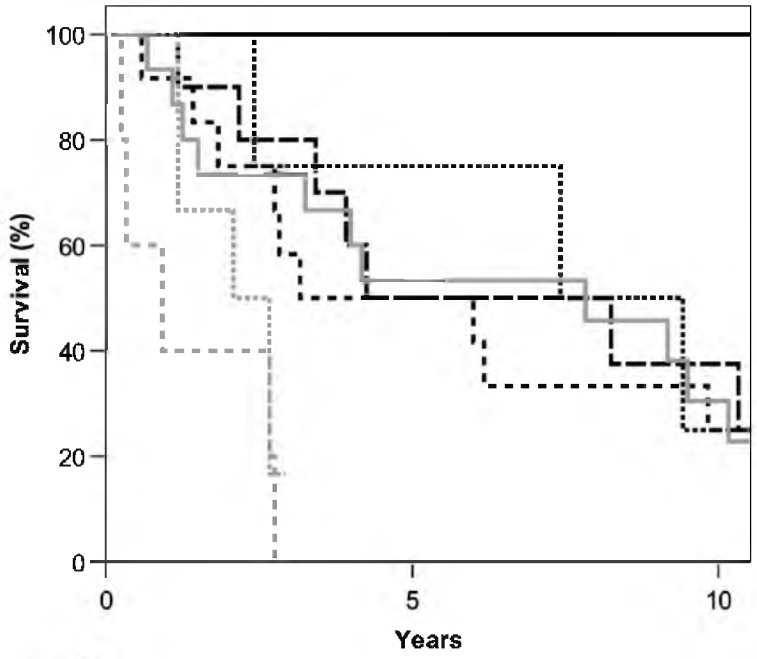
In 22 cases (37%), there was tumor in peritracheal lymphatics on histologic examination (7 cases), a tumor-positive lymph node biopsy was present (9), or both (6). In the other 36 cases (61%), neither lymphatic invasion nor lymph node metastasis was demonstrated. Lymphatic invasion was correlated with the degree of differentiation: histologic lymphatic invasion or tumor positive lymph node biopsies were present in 1 of 14 well differentiated (7%), 13 of 29 moderately differentiated (49%) and 9 of 16 poorly differentiated (56%) tumors ($P = 0.015$). Survival in patients without lymphatic invasion was higher than when lymphatic invasion was present ($P = 0.049$, Figure 3B). There was no difference in survival between patients who had lymphatic invasion only versus patients with positive lymph nodes only, versus both ($P = 0.382$).

Depth of Invasion (Table 2 and Figure 3C)

Carcinomas in situ (level 0) were uncommon, while tumor invaded peritracheal fibroadipose tissue (level 3a) in 16 cases (27%), extended to the soft tissue resection margin (level 3b) in 6 cases (10%), and invaded the thyroid gland (level 4) in 5 cases (8%). While both patients with carcinoma in situ were alive without disease 9.6 and 15 years after resection, there was no difference in survival between levels 1, 2 (a and b) and 3a (Table 1 and Figure 3C). Incomplete resection and involvement of the thyroid gland were both negative prognostic markers: mean survival was 2.1 years in patients with tumor at the soft tissue resection margin (level 3b), and 1.4 years when tumor invaded the thyroid gland (level 4), both significantly lower than in other levels of invasion ($P = 0.025$ and $P < 0.001$, respectively). Lesser levels of invasion were associated with a higher incidence of well differentiated histology ($P = 0.018$) and a lower incidence of lymphatic invasion ($P = 0.002$).

Table 2. Pathologic Characteristics According to Depth of Invasion

			Well Differentiated		Lymphatic Invasion		Tumor thickness > 2 cm	
Depth of invasion	N	%	N	%	N	%	N	%
Level 0	2	3.4	2	100.0	0	0.0	0	0.0
Level 1	5	8.5	2	40.0	0	0.0	0	0.0
Level 2a	14	23.7	5	35.7	1	7.1	0	0.0
Level 2b	11	18.6	4	36.4	5	45.5	2	18.2
Level 3a	16	27.1	1	6.3	7	43.8	6	37.5
Level 3b	6	10.2	0	0.0	4	66.7	1	16.7
Level 4	5	8.5	0	0.0	5	100.0	0	0.0
Overall	59	100.0	14	23.7	22	37.3	9	15.3



Depth of invasion	Number at risk		
Level 0	2	2	1
Level 1	5	3	1
Level 2a	14	6	3
Level 2b	11	5	3
Level 3a	16	8	4
Level 3b	6		
Level 4	5	0	

Figure 3C. Overall survival according to depth of tumor invasion

Tumor Thickness

Mean tumor thickness was 1.3 cm (median 1.1 cm, range 0.1 – 5.5 cm). Tumors were 2 cm or smaller in 85%. Within this range, tumor thickness had no significant impact on survival (*P* = 0.650). Tumors of greater thickness were associated with resections of greater (> 3 cm) length (P = 0.008), although there were two resections of 2.0 and 2.5 cm in length of trachea with a tumor of 3 and 5 cm in thickness, respectively (Figure 4, correlation coefficient 0.364). Tumors > 2 cm in thickness had no different survival than tumors of 2 cm or less (*P* = 0.353). Tumors > 2 cm in thickness more frequently invaded peritracheal fibroadipose tissue (6 of 9, 67%) than smaller tumors (10 of 50, 20%) (*P* = 0.004), but were not associated with level 3b or level 4 (Table 2).

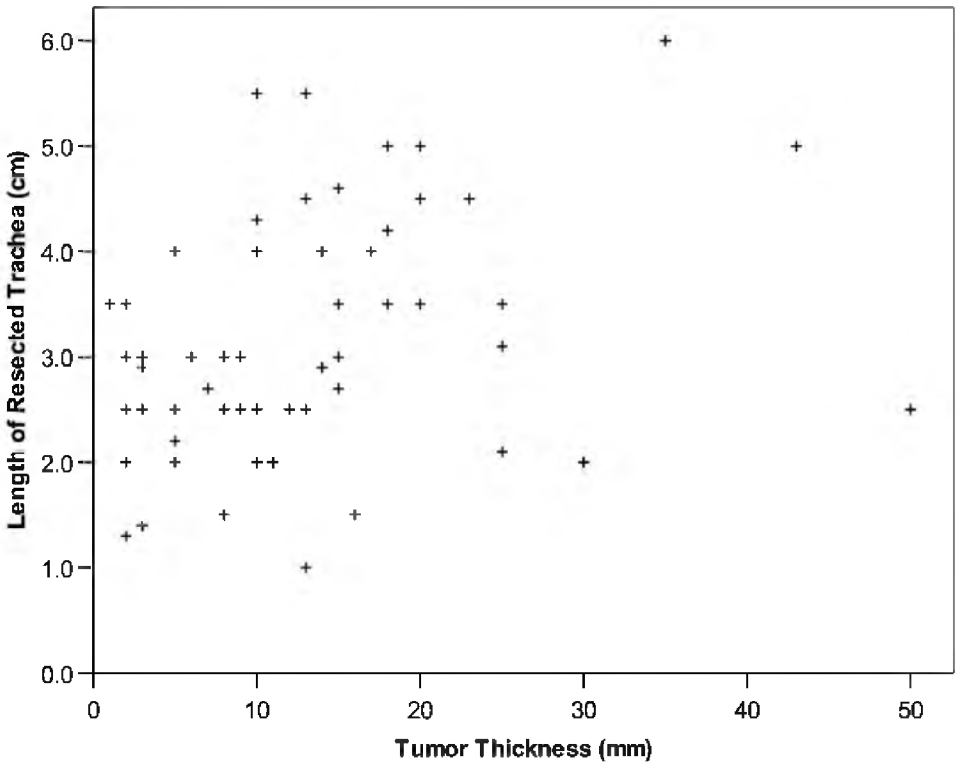


Figure 4. Correlation between thickness and length of resected tracheal tumor. Each data point represents one tumor specimen

Discussion

In this pathologic review of primary tracheal squamous cell carcinoma, the largest series to date, we show that completeness of resection, involvement of the thyroid gland, and lymphatic invasion are histopathologic features with important prognostic value. Increasing depth of invasion into the tracheal wall is associated with a loss of histologic differentiation and lymphatic invasion. Although survival in well differentiated carcinomas is higher, this difference is not significant and may be attributed to the higher incidence of lymphatic invasion in moderately and poorly differentiated carcinomas. Further, we observed that resected tracheal SCCs are mostly small tumors (median thickness 1.1 cm) and that tumor thickness within this range did not significantly affect prognosis. A possible explanation for this finding is that thickness may result from the exophitic portion of the tumor and thus is not conditioned on deeper invasion into the tracheal wall. A higher proportion of larger tumors, however, exhibit lymphatic invasion, a significant predictor of survival.

Surgical resection may lead to excellent survival even when the tumor violates the boundaries of the trachea and invades peritracheal fibroadipose tissue. To provide the best chances of survival, it is however important for the surgeon to achieve negative soft tissue resection margins. When faced with a tracheal SCC growing into the thyroid gland, our findings indicate that surgical resection should be applied to carefully selected patients and palliative therapy may be considered when complete resection is otherwise compromised. Further, the pathologist reviewing

SCC of the trachea should be aware of the importance of lymphatic invasion and specifically investigate the tumor for the presence of this feature.
There are some limitations to our study. We retrospectively analyzed large pathologic specimens of tracheal SCC, and only resected cases were included. Tumors growing into vital organs such as the heart or the great vessels and tumors involving long segments of airway judged unresectable were treated at the Massachusetts General Hospital but are not included in our study. We might have underestimated or misjudged the histologic characteristics, as only a limited number of representative slides for each case were available during histologic review; further, there were only 5 cases with invasion of the thyroid gland.

Tracheal SCC is a rare tumor, and few centers acquire proficiency in its surgical treatment. The dissemination of whatever prognostic information is available assumes therefore a greater importance. We confirm that lymphatic invasion predicts prognosis, while depth of invasion could not be correlated with survival, except for a marked decline when tumor was present at the resection margin or invaded the thyroid gland. We therefore conclude that even in cases where tumor invades peritracheal fibroadipose tissue, excellent survival can be achieved provided the patient undergoes surgical resection and the resection is complete. Positive resection margins in turn predict treatment failure. Our previous report showed that outcome in patients with unresected tumors is worse than in patients that underwent resection [5], a finding supported here by the poor prognosis in patients with incomplete resection. Thus, tumor resectability, usually dictated by tumor length in the long axis of the airway and invasion of vital organs, may possibly be the single most important prognostic factor in this very distinct type of cancer.

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CHAPTER THREE

3.2 – Prognostic Value of Pathologic Characteristics and Resection Margins in Tracheal Adenoid Cystic Carcinoma

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ABSTRACT

Purpose: We wished to investigate the influence of tumor and resection characteristics on survival in adenoid cystic carcinoma (ACC) of the trachea.

Methods: A retrospective study of 12 laryngotracheal, 58 tracheal, and 38 carinal resections for primary ACC in 108 consecutive operative survivors between 1962 and 2007 was conducted. Postoperative radiotherapy was administered to 82% of patients (89/108). Depth of invasion, extramural extent, organ invasion, perineural growth, margin status, and lymph node involvement were described.

Results: Tumor was intramural in 15% (16/108), extramural in 85% (92/108), and invaded adjacent organs in 20% (22/108). Airway margins were grossly positive in 9 (8%), microscopically positive in 59 (55%) and negative in 40 (37%) of 108 resections. Adventitial (radial) margins of transmural sections were grossly positive in 3 (3%), microscopically positive in 95 (88%) and negative in 10 (9%). Perineural growth was present in 37 (34%), absent in 12 (11%) and not observed in 59 (55%). Lymph nodes were positive in 16 (15%), negative in 45 (42%) and not sampled in 47 (44%). Median overall (OS) and disease-free survival (DFS) for the entire group were 17.7 and 10.2 years. OS was longer after resection with negative airway margins (20.4 vs. 13.3 years, $P = 0.028$), negative radial margins (21.7 vs. 13.3 years, $P = 0.050$) and absence of extramural disease (21.7 vs. 13.3 years, $P = 0.007$), perineural growth (22.8 vs. 7.5 years, $P = 0.011$), or lymph node metastases (16.8 vs. 6.1 years, $P = 0.017$). DFS was longer after resection with negative airway margins (16.6 vs. 9.3, $P = 0.005$) and absence of extramural disease (17.9 vs. 9.3 years, $P = 0.008$), perineural growth (17.9 vs. 6.6 years, $P = 0.033$), or lymph node metastases (10.2 vs. 3.0 years, $P = 0.005$).

Conclusions: After tracheal resection for ACC, limited tumor extent and complete resection are associated with longer overall and disease-free survival. Long-term survival (> 10 years), however, is also observed after tracheal resection of locally advanced ACC.

Introduction

Adenoid cystic carcinoma (ACC), the second most common tracheal tumor, is a malignant gland tumor known for its distinct epidemiologic, clinical, pathologic and oncologic characteristics. ACC is not related to smoking, equally distributed among sexes and mean age at presentation is lower than in bronchogenic carcinoma [1]. While patients with ACC of the trachea are usually excellent operative candidates, their tumors often exhibit extensive submucosal and perineural spread. Tumor-free resection margins may therefore be difficult to achieve without excessive anastomotic tension.

Due to insidious growth, prolonged survival may be observed even following palliative treatment. Consequently, long-term follow-up (> 15 years) is important for survival and recurrence analysis.

Complete surgical resection of ACC is associated with long survival [2,3]. The impact of lead-time bias and the role of microscopic tumor at the resection margins or in lymph nodes, however, are less clear than for bronchogenic carcinoma. Regnard and associates [4] described 62 patients with ACC, in whom survival in patients with complete resection was better than in patients with incomplete resection, although this difference was not statistically significant. In the most recent review of MGH data, tumor-positive lymph nodes significantly lowered survival in patients with squamous cell carcinoma, but had no effect on survival in patients with ACC [2]. To further elucidate the impact of pathologic factors on overall and disease-free survival and to assess the role of resection margins and lymph node metastases, a retrospective review of patients with primary ACC of the trachea that underwent resection at our institution was conducted.

Patients and Methods

Patient Selection

A retrospective analysis of all patients with resection for primary ACC of the trachea since 1962 was conducted at Massachusetts General Hospital (MGH). Medical records, Department of Pathology databases and the thoracic surgical database were searched to identify tracheal tumors. Patients who underwent their first resection elsewhere were included if the purpose of the second procedure at MGH was complete tumor excision. Pathology reports, operative reports, and hospital charts were reviewed to exclude laryngeal cancer and tumors of the lung extending to the carina. Because this study aims to investigate disease-specific survival rather than procedure-specific survival, patients who died prior to discharge (operative deaths) were also excluded. The MGH institutional review board approved previous retrospective studies and the most recent protocol (No. 2006-P-002009/3) in March 2008. Consent was received from patients before obtaining follow-up information.

Types of Resection

The surgical technique has been detailed previously [5]. Resections were grouped by anatomic region and extent. The trachea was divided into three parts from the cricoid to the carina. The location was recorded as proximal when tumor occupied the distance from cricoid to 3 centimeters below the cricoid and distal from the carina to 3 centimeters above the carina, while tumors located between proximal and distal were labeled middle. Designations of tumor location made by the airway surgeon were followed when applicable.

For standard tracheal resection, a sleeve of trachea was removed with end-to-end reconstruction. When tracheal resection was combined with laryngectomy, cervical or mediastinal end-tracheostomy was required. For laryngotracheal resection, the tumor was removed with a portion of infraglottic larynx while preserving at least one recurrent laryngeal nerve not involved with tumor. Reconstruction was achieved by shaping the remaining trachea to conform to the laryngeal defect. Carinal resection was performed with or without concomitant lung resection. Carcinomas involving the carina by extension from the lung or a mainstem bronchus were excluded from analysis. Systematic lymph node dissection was assumed to interfere with the tracheal blood supply and was therefore not performed. Regional lymph nodes were often not included in the specimen if not grossly enlarged. Absence of tumor at the airway margins was confirmed by frozen section unless the limits of resection had been reached and no additional trachea could be removed.

Tumor Data

Operative and pathology reports were reviewed for the assessment of airway and adventitial margins of transmural sections (radial margin). Resection margins were regarded as grossly positive when visible tumor was noted by surgeon or pathologist. Tumor dimension in the long axis of the airway, extramural invasion, perineural growth, lymph node metastases and the presence of microscopic tumor at airway and radial resection margins were recorded as noted in the pathology report. Microscopically positive airway margins indicated true residual tumor by pathologic evaluation. In contrast, the radial margins were interpreted as microscopically positive when tumor was within 1 mm of the margin, usually indicating that only a thin layer of connective tissue covered the outside of the tumor. Extension through the tracheal adventitia was recorded as extramural invasion.

Adjuvant Radiotherapy

Adjuvant postoperative radiotherapy was introduced for malignant tumors during the second decade of this experience for close or tumor-bearing margins. After bronchoscopic assessment of anastomotic healing, a recommended dose of 54 Gy was administered 6 to 8 weeks after resection. Most patients received radiation treatment outside Massachusetts General Hospital.

Follow-Up

Patients and their physicians were contacted for follow-up information. The Social Security Death Index was searched. Patients were determined to have died if name, date of birth, and social security number matched. Patients were judged to have recurrent disease when proven by biopsy or clinically suspect recurrence was present. The survival period began on the day of operation. Recurrent disease or death concluded the disease-free survival.

Statistical Analysis

In contrast to the earlier report that used an actuarial method [2], median overall and disease-free survival after airway resection were calculated using the Kaplan-Meier procedure with the log rank test implemented in the SPSS 14.0 statistical software program (SPSS Inc, Chicago, IL). Categorical variables were compared with the Chi-Square test.

Results

Between 1962 and March 2008, 117 patients with primary adenoid cystic carcinoma of the trachea underwent surgical resection. Nine operative deaths, six of these after carinal resection, were excluded. The cause of death was related to the anastomosis in 5 patients and to respiratory failure in the other 4.

Table 1. Tumor Localization and Types of Operation

	n	%
Tumor localization in trachea		
Proximal	23	21
Middle	27	25
Distal	58	54
Type of operation		
Laryngotracheal	12	11
Tracheal	51	47
Tracheal with permanent tracheostomy	7	6
Carinal without pulmonary resection	26	24
Carinal with pulmonary resection	12	11
Total	108	100

Table 2. Pathologic Characteristics in 108 Cases of Adenoid Cystic Carcinoma

	n	%
Airway resection margins		
Grossly positive	9	8
Microscopically positive	59	55
Negative	40	37
Radial resection margins		
Grossly positive	3	3
Microscopically positive	95	88
True positive	78	72
Within 1 mm	17	16
Negative	10	9
Extramural extent		
Yes	92	85
No	16	15
Invading adjacent organ(s)		
Yes	22	20
Esophageal muscle layer	16	15
Thyroid gland	10	9
Recurrent laryngeal nerve	7	6
Strap muscles	4	4
Great vessels	1	1
Pericardium	1	1
No	86	80
Perineural growth		
Yes	37	34
No	12	11
Not noted in pathology report	59	55
Lymph node invasion		
Yes	16	15
No	45	42
No lymph nodes sampled	47	44
Total	108	100

Overall Characteristics

There were 46 men (43%) and 62 women (57%) with a mean age of 48 years (range, 24 to 80 years). Tumor localization and type of operative treatment are shown in Table 1. More than half of all tumors were localized in the distal part of the trachea, requiring carinal resection in two-thirds. Laryngotracheal resection for ACC was performed in 11% (12/108) of cases. In only 7 cases (6%), a permanent tracheostomy resulted from resection (laryngectomy in 4, cervical exenteration in 2 and tracheal resection with permanent tracheostomy in 1). Mean length of resected airway was 4.1 cm (range, 1.5 to 8.0 cm).

Postoperative radiation was confirmed in 82% of patients (89/108). Seventeen of 19 patients who did not undergo postoperative radiation had microscopically positive

radial margins, while 6 of the 17 had also microscopically positive airway margins and 1 a grossly positive airway margin. Between patients with and without postoperative radiation, median survival (17.7 vs. 16.8 years, $P = 0.81$) and disease-free survival (10.3 vs. 4.3 years, $P = 0.68$) did not differ significantly.

Overall Survival and Disease-Free Survival

Mean follow-up in 108 cases was 8.6 years (range, 0 months to 32.5 years). Survival follow-up was complete in 59% of patients (64/108), and disease-free survival follow-up in 66% (71/108). Median survival was 17.7 years and 5-, 10-, 15- and 20-year survival were 78%, 65%, 53% and 43%, respectively. Median disease-free survival was 10.2 years and 5-, 10-, 15- and 20-year disease-free survival were 67%, 53%, 38% and 26%, respectively.

Information derived from pathology reports is detailed in Table 2. Survival and disease-free survival data in all pathologic subgroups are shown in Table 3 and Figures 1 (A – E) and 2 (A – C).

Airway resection margins

Grossly positive airway margins occurred in less than 10% of cases. Survival was significantly lower in patients with gross positive airway margins ($P = 0.026$). In patients with negative gross airway margins, pathologic examination of the airway resection margins revealed microscopic tumor presence in a little more than half of cases.

As depicted in Figure 3A, the presence of gross or microscopic tumor at the airway resection margins was related to length of resection, although not in a linear manner. After resection of up to 4.6 cm in length, margins were either grossly or microscopically positive in 56% (44/78), compared to 80% (24/30) in resections of greater length ($P = 0.023$).

Grossly positive tracheal margins had a marked early negative impact on overall survival (Table 3), while the survival of patients with microscopic positive airway resection margins decreased and separated from the group with microscopic negative airway margins only beyond 15 years (Figure 1A). A distinct advantage in disease-free survival was found in favor of tumors with negative airway resection margins compared to positive gross and microscopic airway margins, clearly separating after 10 years (Figure 2A).

Radial resection margins

Negative gross radial margins were obtained in all but 3 patients and in these, airway margins were also grossly positive. However, radial resection margins were microscopically close in nearly 90% of cases.

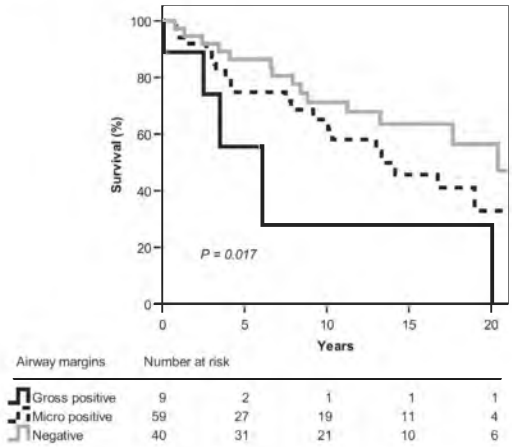
Table 3. Overall and Disease-Free Survival According to Pathologic Subgroups

Pathologic subgroup	N	Median survival (years) 95% CI	P	Survival (%) 5-yr	10-yr	15-yr	20-yr	Median DFS (years) 95% CI	P	Disease-Free Survival (%) 5-yr	10-yr	15-yr	20-yr
Airway resection margins													
Grossly positive	9	6.1 (2.1-10.1)		56	28	28	28	2.6 (1.2-4.0)		31	31	31	31
Microscopically positive	59	13.3 (6.7-20.0)	*	75	65	46	33	9.7 (7.8-11.5)	†	66	48	24	7
Negative	40	20.4 (15.4-25.4)		86	71	64	57	16.6 (6.7-26.5)		76	63	56	50
Radial resection margins													
Grossly positive	3	2.5 (na)		50				2.3 (na)		50			
Microscopically positive	95	13.3 (7.5-19.2)	0.050	77	62	47	36	9.7 (7.3-12.1)	0.090	64	50	33	25
Negative	10	21.7 (20.1-23.2)		100	100	100	100	17.9 (15.2-20.7)		100	86	86	43
Extramural extent													
Yes	92	13.3 (8.9-17.6)	0.007	74	60	44	35	9.3 (7.1-11.4)	0.008	61	47	29	22
No	16	21.7 (na)		100	93	93	80	17.9 (11.1-24.7)		100	93	85	49
Invading adjacent organ(s)													
Yes	22	10.3 (4.1-16.5)	0.257	69	52	31	31	3.0 (0.0-6.4)	0.167	44	44	33	16
No	86	19.0 (13.4-24.8)		81	68	57	46	11.2 (7.2-15.2)		73	55	39	29
Perineural growth													
Yes	37	7.5 (4.6-10.4)	0.011	62	40	23	23	6.6 (2.3-10.9)	0.033	51	33	27	13
No	12	22.8 (na)		91	91	91	78	17.9 (16.1-19.8)		92	80	80	32
Not noted in report	59	19.0 (12.6-25.4)		86	73	58	46	11.9 (8.0-15.8)		72	58	35	31
Lymph node invasion													
Yes	16	6.1 (1.4-10.8)	0.017	54	32	16	16	3.0 (2.1-3.9)	0.005	34	7		
No	45	16.8 (10.7-22.8)		76	66	54	38	10.2 (6.7-13.7)		63	56	33	20
No lymph nodes sampled	47	21.6 (10.2-33.0)		91	80	71	71	18.4 (10.8-26.0)		86	71	62	47
Overall	108	17.7 (12.0-23.3)		78	65	53	43	10.2 (7.4-12.9)		67	53	38	26

*Negative versus positive (n=68), $P = 0.028$. Gross positive versus gross negative (n=99), $P = 0.026$. Microscopic positive versus negative, $P = 0.069$. All three compared (Figure 1A), $P = 0.017$

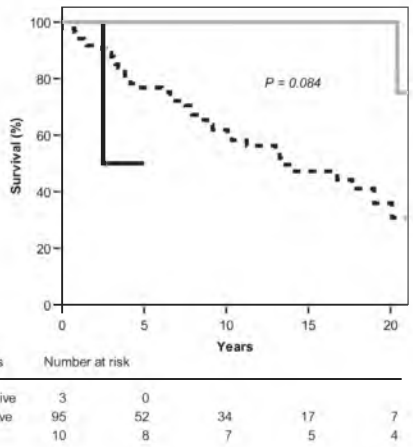
†Negative versus positive (n=68), $P = 0.005$. Gross positive versus gross negative (n=99), $P = 0.074$. Microscopic positive versus negative, $P = 0.012$. All three compared (Figure 2A), $P = 0.010$

Figure 1A



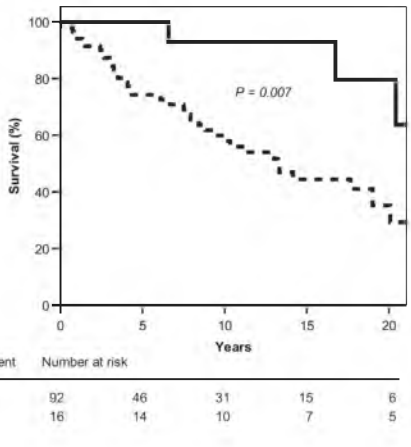
Airway margins	Number at risk				
Gross positive	9	2	1	1	1
Micro positive	59	27	19	11	4
Negative	40	31	21	10	6

Figure 1B



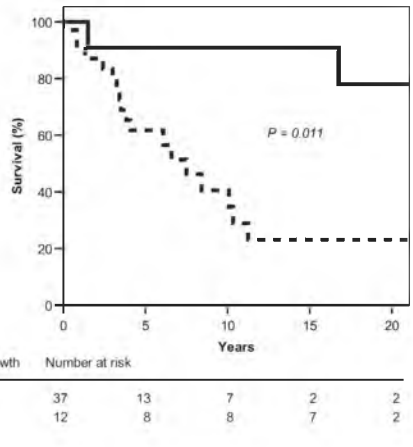
Radial margins	Number at risk				
Gross positive	3	0			
Micro positive	95	52	34	17	7
Negative	10	8	7	5	4

Figure 1C



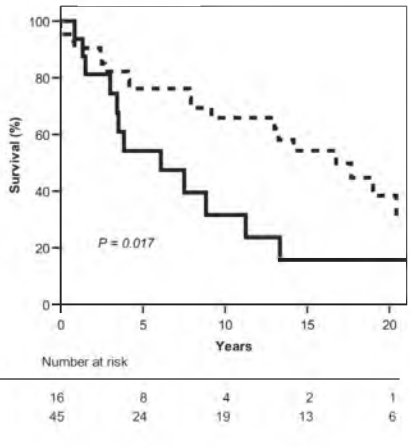
Extramural extent	Number at risk				
Yes	92	46	31	15	6
No	16	14	10	7	5

Figure 1D



Perineural growth	Number at risk				
Yes	37	13	7	2	2
No	12	8	8	7	2

Figure 1E



Lymph nodes	Number at risk				
Positive	16	8	4	2	1
Negative	45	24	19	13	6

Figure 1. Survival in resected adenoid cystic carcinoma by A. Airway margins; B. Radial margins; C. Extramural extent; D. Perineural growth; E. Lymph node invasion

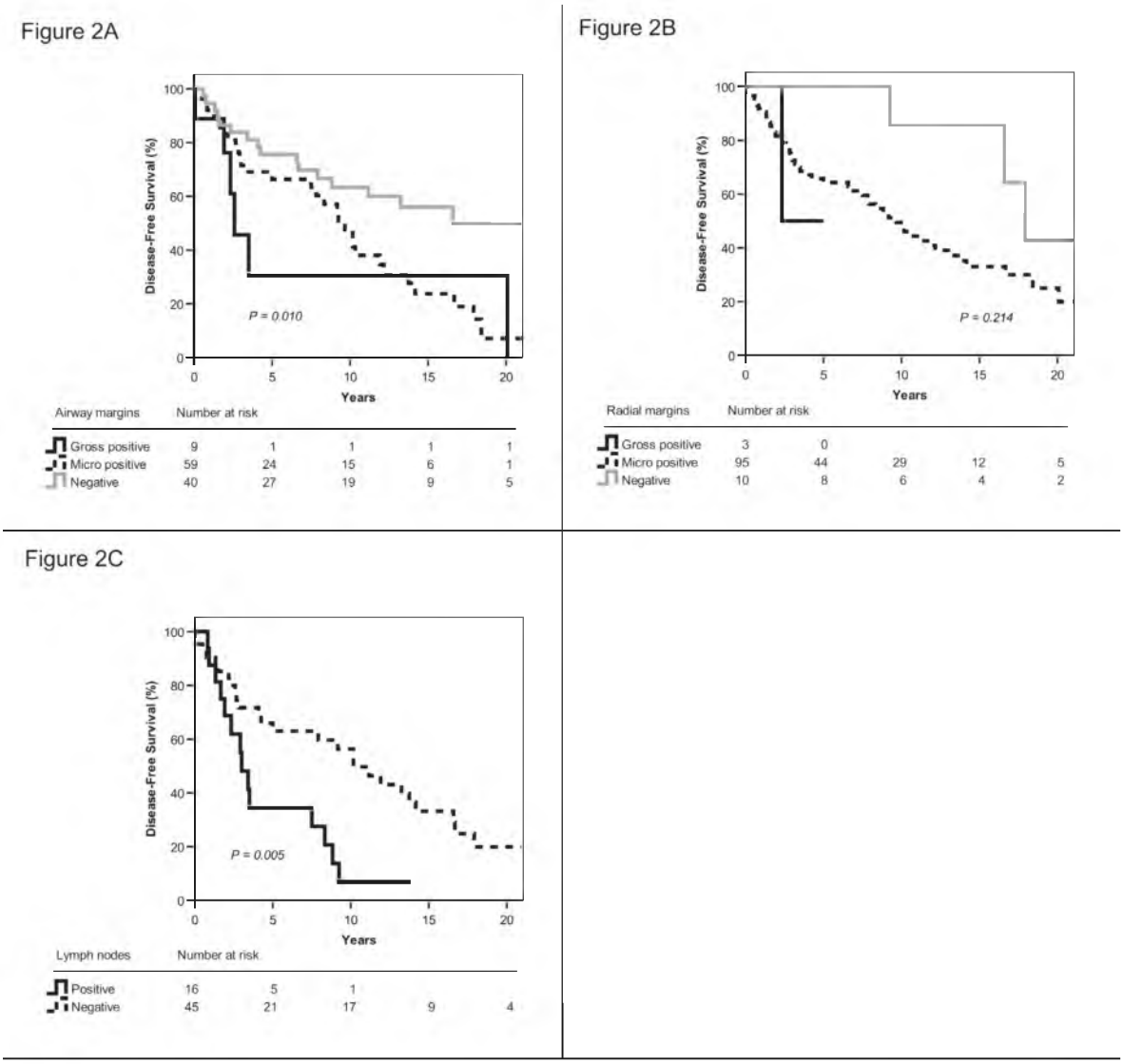


Figure 2. Disease-free survival in resected adenoid cystic carcinoma by A. Airway margins; B. Radial margins; C. Lymph node invasion

The length of resected airway correlated with the presence of tumor at the radial margins (Figure 3B). In resections less than 4.6 cm in length, radial margins were either grossly or microscopically positive in 88% (69/78), compared to 97% (29/30) in resections of greater length (P = 0.19).

Median overall survival in patients with negative radial resection margins, with tumor contained by tracheal adventitia, was higher than in patients with microscopically positive resection margins (21.7 vs. 13.3 years, P = 0.050, Figure 1B). Disease-free survival in patients with negative radial margins was also higher (P = 0.090, Figure 2B). The small sample size did not allow comparisons with gross radial resection margins. Within the subgroup of cases with microscopically positive radial resection margins, there were no differences in survival (P = 0.38) or disease-free survival (P = 0.19) between true positive margins (n = 78) and tumor within 1 mm of the radial resection margin (n = 17).

Figure 3A

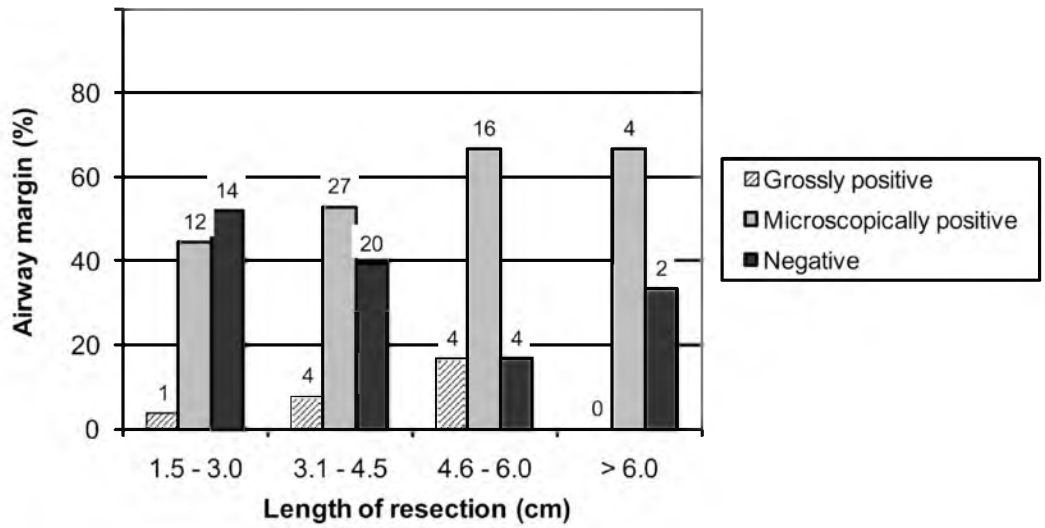


Figure 3B

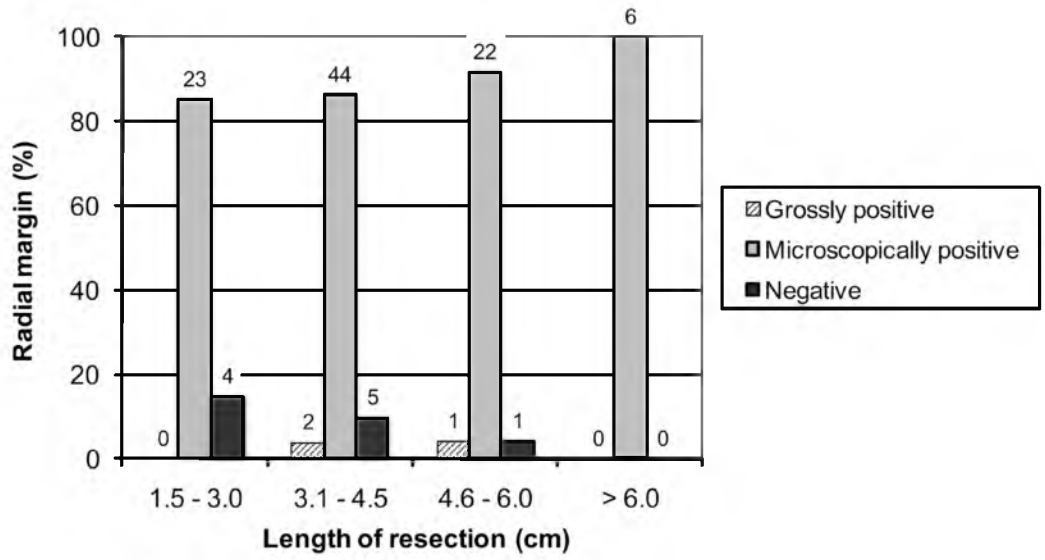


Figure 3. Resection margins by length of resection. A. Airway resection margins; B. Radial resection margins

Extramural Extent

More than 80% of tumors grew through the tracheal wall beyond the adventitia. Since radial margins are limited by the presence of essential adjacent organs, extramural tumor presence was almost always accompanied by exceedingly close, or positive, radial resection margins. Invasion through the adventitia was a significant prognostic factor for both overall survival (Figure 1C) and disease-free survival. Mean overall survival and disease-free survival in 20 tumors without extramural extent exceeded 20 years, and their 20-year survival was 72%.

Invasion of Adjacent Organs
In most cases of organ invasion, more than one organ was invaded, typically a combination of thyroid gland and esophageal muscle coat. Organ invasion did not impact overall (P = 0.26) or disease-free survival (P = 0.17) if all gross tumor was removed.

Perineural Growth
The pathology report included a statement on the presence or absence of perineural growth in 46% (49/108), and in 37 of these (76%), there was perineural growth. Absence of perineural invasion was specifically observed in only 11% of pathology reports (12/108). The presence of perineural growth decreased both overall survival (Figure 1D) and disease-free survival. In cases where the absence of perineural growth was recorded, survival (P = 0.18) and disease-free survival (P = 0.11) were similar to cases in which no statement on perineural growth was included in the pathology report.

Lymph Node Invasion
Lymph nodes were sampled in 57% of resected tumors (61/108) and found to be positive in 26% (16/61). The lymph node stations in these 16 cases were paratracheal in 9, paratracheal and hilar in 3, subcarinal in 2, and hilar only in 2. Overall survival (Figure 1E) and disease-free survival (Figure 2C) were significantly lower in patients with lymphatic invasion. No significant survival differences existed between patients with negative and without sampled lymph nodes.

Discussion

This study describes the influence of pathologic characteristics on long-term survival in a consecutive series of patients undergoing surgical treatment for primary tracheal ACC. Our most recent review included analysis of prognostic value of lymph node status in 96 cases of ACC and airway resection margins in 82 cases using an actuarial survival analysis [2]. In the current review, new cases were added, follow-up was updated and operative deaths were excluded. We analyzed survival and disease-free survival in 108 cases of resected ACC using the Kaplan-Meier method according to detailed review of airway and radial resection margins, extramural extent, invasion of adjacent organs, perineural growth and lymph node status.

Airway and radial resection margins were important prognostic factors for both survival and disease-free survival. Patients with grossly positive airway margins had significantly worse survival than patients with grossly negative resection margins. Microscopically positive airway margins, present in nearly half of all patients, were associated with lower survival and correlated with poorer disease-free survival. Due to the high rate of extramural extent, microscopically positive radial resection margins occurred in 88% of patients. Positive microscopic radial margins, probably a surrogate for larger tumor mass in this study, led to a significant decline in both

survival and disease-free survival. Invasion of adjacent organs did not seem to affect survival. En bloc resection of invaded organs, such as the thyroid or the esophageal muscle coat, resulted in acceptable long-term survival, as long as negative radial margins can be obtained. In the multi-institutional study by the French Society of Thoracic and Cardiovascular Surgery [4], 5-year survival was 82% in 36 patients with complete resection for ACC, and 63% in 26 patients with incomplete resection. This and another study of 29 cases of resected ACC [6] document the difficulties of establishing statistically significant observations in this rare tumor. The limited follow-up period may have been inadequate to demonstrate meaningful differences in survival.

Regnard and associates reported that there was no correlation between survival and lymph node status in either tracheal ACC or non-ACC tracheal cancer [4]. In our previous report [2], lymph node-positive SCC had a markedly lower survival than tumors without nodal metastasis, while in ACC, no such difference was observed. In the current series, to assess the impact of lymph node status on survival, only lymph-node biopsied patients were compared. Patients with lymph node metastasis had a markedly lower overall and disease-free survival than patients with negative lymph node biopsies. As demonstrated in Table 3, survival of patients who did not have any lymph nodes sampled was comparable to that of patients with negative sampled lymph nodes. A lack of difference here may be explained by the limited information gained from non-systematic lymph node sampling alone: both groups of patients may contain similar proportions of undisclosed lymph node disease.

Another important prognostic factor was perineural growth. Although widely reported as predictor of tumor aggressiveness and survival in head and neck and bronchial carcinoma, the impact of perineural invasion has not previously been described for tracheal carcinoma. The presence or absence of perineural growth was not noted in the pathology report in 55% (59/108) of patients. Most likely, in cases where perineural growth was present, the pathology report included a statement on this feature. The absence of this growth characteristic, however, was probably lacking in around half of all cases. This is supported by the distinct difference in survival between cases where perineural invasion was present and those where either no statement on perineural invasion was present in the pathology report or perineural growth was absent. In these latter two groups, overall and disease-free survival was similar in length. Given its importance, we recommend to always include a statement regarding perineural growth in the pathology reports describing all specimens of tracheal tumors.

Since both perineural growth and extramural extension through the tracheal adventitia were important prognostic factors, these should likely be incorporated in any staging system of tracheal ACC. Both currently proposed non-validated staging guidelines for tracheal cancer are however TNM-based [7,8], leading to greater emphasis on lymph nodes although systematic lymph node sampling should not be part of resection to preserve tracheal blood supply. In the absence of systematic

lymph node sampling, it is important for the surgeon to resect visibly enlarged lymph nodes and for the pathologist to thoroughly examine the paratracheal tissue of the resected tracheal segment for the presence of lymph node tissue and lymphatic spread.

When frozen section reveals microscopic tumor at the tracheal margin, complete resection would demand further shortening of the trachea in order to reach tumor-free tracheal wall as long as anastomotic tension is modest. Since failure of the anastomosis may lead to dehiscence, if not death, in patients with a slow-growing malignancy, a microscopically positive resection margin may have to be accepted. The survival analysis in this study has shown that patients undergoing tracheal resection for ACC with negative and microscopically positive airway margins have a good long-term prognosis, while survival is short when residual gross tumor remains. Thus, surgical resection of the tumor remains the treatment of choice in this rare airway tumor.

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CHAPTER FOUR

4.1 – Incidence and Treatment of Tracheal Cancer: A Nationwide Study in the Netherlands

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ABSTRACT

Background: The aim of this study was to assess the incidence, characteristics, treatment and survival of patients with tracheal malignancies in the Netherlands.

Methods: All cases of tracheal cancer entered into the database of the Netherlands Cancer Registry in the period 1989–2002 were selected. Data on histologic type, age at time of diagnosis, treatment and survival were analyzed retrospectively.

Results: The annual incidence was 0.142 per 100,000 inhabitants (308 cases, of which 15 were found incidentally at autopsy). Of these, 72% were men. In 52.9% the histologic type was squamous cell carcinoma and in only 7.1% adenoid cystic carcinoma (ACC). Mean age at time of diagnosis was 64.3 years. Of the 293 patients diagnosed while alive, 34 patients underwent surgical resection (11.6%), 156 patients received radiotherapy (53.2%), and 103 patients neither (35.4%). Median survival of all 293 patients was 10 months (mean 28 months) with 1-year, 5-year and 10-year survival rates of 43%, 15% and 6%, respectively. The prognosis of patients with ACC was significantly better. The 5-year survival rate in patients who underwent surgical resection was 51% and the 10-year survival rate in these patients was 33%.

Conclusion: The prognosis of patients with a tracheal malignancy is usually poor. Surgical treatment, however, can lead to good survival rates; still, this is currently only used in selected patients, even though it would seem to be possible in more cases in view of the technical advances in the field of tracheal surgery. Centralizing the care and treatment of tracheal cancers and implementing a more assertive attitude towards this disease could make surgery accessible to a larger number of patients. Data from the literature show that this would lead to a better survival in patients with a tracheal malignancy.

Introduction

Primary tracheal cancer is rare and its incidence is very low compared with laryngeal or bronchial cancer. The annual incidence of tracheal cancer is approximately 0.1 per 100,000 persons [1,2], accounting for only 0.2% of malignant neoplasms of the respiratory tract [3,4] and only 0.02–0.04% of all reported malignancies [1,5]. Because of its low incidence, knowledge of the epidemiology, etiology, prognostic factors and methods of treatment is limited. Tracheal cancer is more common in men and patients with a history of smoking, the latter group making up 77–86% of all patients with tracheal cancer. Median age at the time of diagnosis is 67 years [5,6]. The prognosis of patients diagnosed with tracheal cancer is poor, the 5-year survival rate being 5–35% [2,5-8].

Surgery with or without irradiation is considered to be the treatment of choice [2,6,9-12] for two histologic types of primary tracheal carcinoma, with different characteristics: squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC) [6,7,10,11,13]. Licht et al. (2001) concluded that a nihilistic attitude exists, based on ignorance of the surgical treatment of tracheal cancers. In Denmark, less than 10% of all patients with tracheal cancer were treated surgically, whereas patients undergoing this type of treatment had better survival rates compared with patients undergoing other types of treatment [5]. These findings are in line with those of Manninen et al. in 1993 [6]. If ignorance of surgical treatment is so widespread, the management of tracheal cancer could certainly be improved. A more aggressive approach towards tracheal cancer might lead to improved survival in patients diagnosed with this disease.

In the Netherlands, all hospitals are associated with one of the nine regional cancer registries (Comprehensive Cancer Centers), which submit their data to the national database of the Netherlands Cancer Registry (NCR), thus creating a systematic collection of data on all malignant neoplasms occurring in the Netherlands since 1989. This provides the prerequisites for a reliable nationwide study on tracheal cancer. The goal of this study was to assess the incidence, characteristics, treatment modalities and treatment outcome of tracheal cancer in the Netherlands.

Materials and Methods

In the Netherlands, a population-based cancer registry exists. Nine regional cancer registries gather data on patient characteristics, topography, morphology, stage and treatment of cancer. The main source of notification is a national archive of pathology reports. This is completed with data from the National Hospital Discharge Registry. After notification, specially trained registrars collect data from the patient files in the hospitals.
For the current study, all cases of primary tracheal cancer reported in the files of the Netherlands Cancer Registry (NCR) between 1989 and 2002 were selected. The regional cancer registries provided data on patient characteristics, clinical

information, pathologic data and treatments given with regard to the tracheal cancer, as well as the occurrence of other malignant tumors before or after the diagnosis of tracheal cancer. For these other tumors, the localization, histologic type and date of diagnosis were recorded. Furthermore, the date of death was recorded and, if not applicable, the date of the most recent follow-up. All data were stored in a database designed especially for the study.

The annual incidence as an average over the 14-year period was calculated using data from Statistics Netherlands (Centraal Bureau voor de Statistiek, CBS). During the period of the study, the number of inhabitants in the Netherlands increased from 14.8 million in 1989 to 16.1 million in 2002. The average size of the population in this period was 15.4 million. Survival was calculated from the time of diagnosis until the last follow-up and analyzed using the Kaplan-Meier procedure with the log-rank test to compare survival functions. Statistical analysis was performed using the statistical program SPSS 12.0.1.

Results

During the 14-year period between 1989 and 2002, 312 cases of tracheal cancer were reported in the files of the Netherlands Cancer Registry. After reviewing the tumor localization, four patients were excluded, of which two had a lymphoma, one a laryngeal carcinoma and one a bronchial carcinoma. Finally, 308 cases were regarded as true cases of primary tracheal cancer and included for further investigation. These cases accounted for 0.034% of all recorded malignancies in this period. The calculated annual incidence in this period is 0.142 per 100,000 inhabitants.

Table 1. Histologic Types in 308 Tracheal Cancer Cases in the Netherlands

Histologic type	n	%
Squamous cell carcinoma (SCC)	163	52.9
Small cell carcinoma	34	11.0
Epithelial large cell carcinoma	23	7.5
Adenoid cystic carcinoma (ACC)	22	7.1
Adenocarcinoma	19	6.2
Carcinoid	4	1.3
Papillary SCC	2	0.6
Neuroendocrine carcinoma	2	0.6
Mucinous adenocarinoma	2	0.6
Adenosquamous carcinoma	2	0.6
Malignant melanoma	2	0.6
Carcinoma, not otherwise specified	24	7.8
Other	9	2.9
Total	308	100.0

Seventy-two percent of all tracheal cancers were diagnosed in men (n=223) and 28% in women (n=85). The most common histologic type was SCC, which was observed in 52.9% of all patients (n=163). The distribution of all histologic types is shown in Table 1. In patients with ACC, the male/female ratio was 1:1 but all other histologic types of tracheal cancer were found predominantly in males.
Fifteen cases (4.9%) were found incidentally at autopsy and 293 were diagnosed while the patients were alive and confirmed by histopathologic examination. This latter group was used for a more detailed analysis and investigation of the age characteristics, treatment modalities and survival outcome.
The mean age at diagnosis was 64.3 years (range 30–95 years). An analysis of the relationship between histologic type and age revealed a lower age at diagnosis for ACC (mean 59.5 years) compared to patients with SCC (mean 64.7 years, Table 2); this difference was almost significant (p=0.054).

Table 2. Age According To Gender And Histologic Type

	n	Mean age (in years)	Range
Overall	293	64.3	30 - 95
Sex			
Male	213	64.5	30 - 95
Female	80	63.8	35 - 89
Histologic type*			
SCC	156	64.7	35 - 95
Small cell carcinoma	32	65.9	43 - 87
Epithelial large cell carcinoma	23	62.5	45 - 79
ACC	21	59.5	38 - 93
Adenocarcinoma	19	61.4	31 - 88
Other	42	66.2	30 - 89

* *P*-value 0.054
SCC = squamous cell carcinoma; ACC = adenoid cystic carcinoma

Thirty-four (11.6%) of the 293 patients underwent surgical resection as the primary treatment; of these, 23 received additional radiotherapy. One of these 23 cases also underwent endobronchial laser therapy. Radiotherapy as the primary treatment was given to 156 (53.2%). Additionally, 12 of these 156 patients received some form of endobronchial treatment, focused mainly on tumor reduction, and another 12 patients received chemotherapy. Of the remaining 103 patients (35.2%) who did not receive either radiotherapy or surgery, 20 patients were treated with chemotherapy and 10 received endobronchial treatments such as laser therapy with palliative intent.

Table 3. Localizations of Prior, Concurrent and Second Primary Tumors (N=85)

Localization	n	%
Bronchus/lung	46	45.5
Head & neck	17	16.8
Skin	11	10.9
Bladder	4	4.0
Esophagus	4	4.0
Breast	4	4.0
Thyroid gland	3	3.0
Trachea	2	2.0
Stomach	2	2.0
Other	8	7.9
Total	101	100.0

Eighty-five patients (29%) had a total of 101 other primary malignancies (Table 3) before or after their tracheal cancer was diagnosed (a mean of 1.2 other primary malignancies per person). Of these tumors, 56% were SCC and 12% were adenocarcinoma. Seventy-three of these other primary tumors were found before the carcinoma in the trachea, 20 were diagnosed in the same year and eight were discovered after the diagnosis of tracheal cancer. More than half of these second primary tumors were located in the respiratory tract.

Table 4. Survival in Tracheal Cancer According to Histologic Type and Type of Treatment

			Survival (months)		Survival rates (%)			
		n	Median	Mean	1-year	2-year	5-year	10-year
Histologic type*	SCC	156	10	24	45	29	12	0
	ACC	21	- †	107	95	89	61	61
	Other types	116	7	18	32	17	9	3
Treatment*	None / other	103	3	13	25	17	4	3
	Radiotherapy	156	11	24	47	27	11	0
	Surgery	34	82	79	79	69	51	35
Overall		293	10	28	44	29	15	6

* *P*-value < 0.0001

† More than 50% of patients with ACC are alive at date of follow-up

SCC = squamous cell carcinoma; ACC = adenoid cystic carcinoma

The 10-year follow-up is complete in 223 of 293 patients (76.1%). The overall median survival (n=293) was 10 months (mean 28 months) with a 1-year survival rate of 43%, a 5-year survival rate of 14% and a 10-year survival rate of 6% (Table 4 and Figure 1). Surprisingly, the survival of patients who had one or more other primary tumors (n=85) was not significantly different from that of patients without other primary tumors (n=208): median survival times of 16 months (95% CI 9–23 months) and 8 months (95% CI 5–11 months), respectively (p=0.0896). The survival following different methods of treatment did differ and was significantly better after surgery (p<0.0001, Table 4). For surgically treated patients without radiotherapy (n=11), the median survival was 91 months (mean 79 months). When surgery and radiotherapy were combined, median survival was 82 months (mean 80 months). Overall, for surgically treated patients (n=34), median survival was 82 months (mean 79 months). Patients treated with radiotherapy alone had a median overall survival

Figure 1.

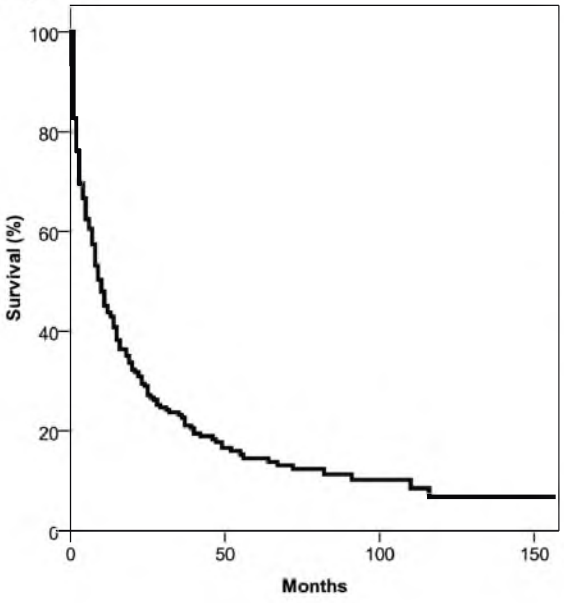


Figure 2.

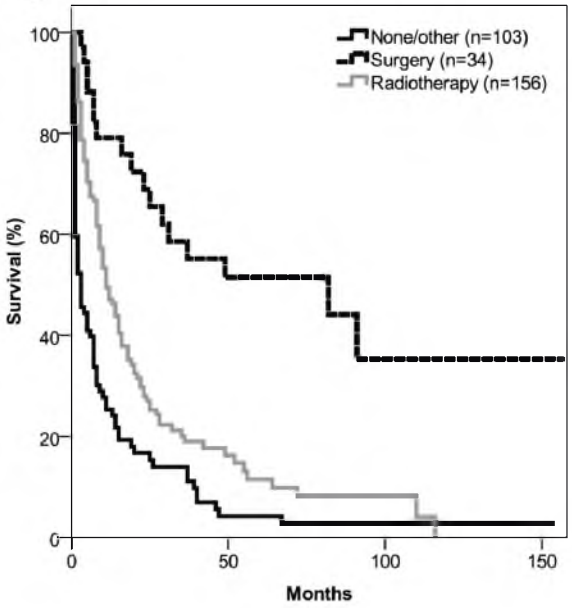


Figure 3.

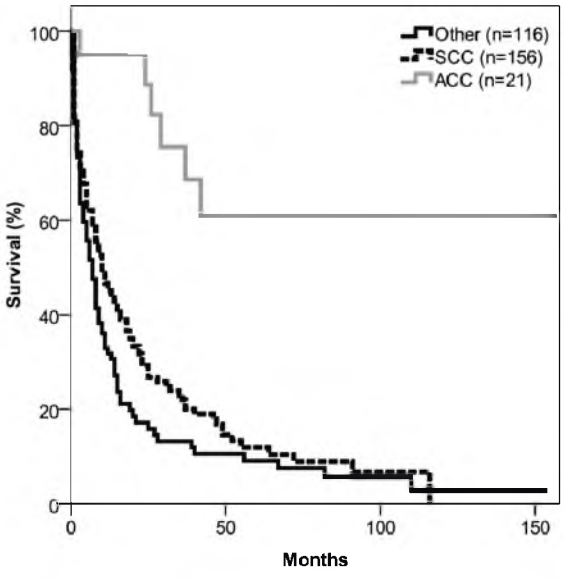
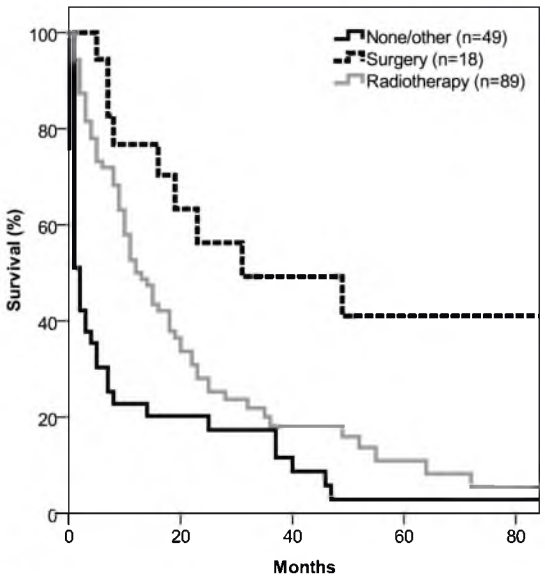


Figure 4.



Figures 1-4. Survival in months. 1. Overall survival of tracheal cancer in the Netherlands (n=293); 2. Survival by treatment; 3. Survival by histologic type; 4. Survival in patients with SCC (n=156) by treatment. SCC = squamous cell carcinoma; ACC = adenoid cystic carcinoma

time of 11 months (median 24 months). In the group of patients who did not receive either surgical treatment or radiotherapy the median survival time was 3 months (mean 13 months). The 5-year overall survival rates were 51% for patients who underwent surgical treatment, 11% for patients treated with radiotherapy alone and only 5% for patients who received neither surgery nor radiotherapy. In the latter group, there were no differences in survival between patients treated with chemotherapy, laser therapy or who received no treatment. Ten years after diagnosis, only three of the 260 patients who were not treated surgically were alive.

The 10-year overall survival rate for patients treated surgically, with or without radiotherapy, is 33% (Figure 2).

Except for ACC, there were no significant differences in survival between the different histologic types. The survival of patients with ACC was significantly better than that for all other histologic types ($p<0.0001$, Table 4 and Figure 3). Eleven (52.4%) of 21 cases of ACC underwent surgery, which was combined with radiotherapy in eight. These 11 cases made up 32.4 % of all surgically treated patients. Other histologic types in this group included eighteen patients with SCC (52.9%), two epithelial large cell carcinomas (5.9%), one carcinoid (2.9%), one epithelial-myoepithelial carcinoma (2.9%) and one malignant melanoma (2.9%).

The differences in survival following different methods of treatment were also investigated in the histologically homogeneous group of patients with SCC who were alive at diagnosis (n=156). The survival time within this group in relation to method of treatment showed nearly the same outcome per treatment modality as the overall outcome ($p<0.0001$, Table 5 and Figure 4). Survival of patients treated with surgery only (n=5) and patients treated with surgery and radiotherapy (n=13) did not differ significantly (median 49 months and median 23 months respectively).

Table 5. Survival in Tracheal Squamous Cell Carcinoma By Type of Treatment (P<0.0001)

		Survival (months)		Survival rates (%)	
Treatment	n	Median	Mean	1-year	5-year
None / other	49	2	11	23	3
Radiotherapy	89	13	24	50	11
Surgery	18	31	49	77	41
Total	156	10	24	45	12

Discussion

In this study, data from the Netherlands Cancer Registry (NCR) were used and reviewed retrospectively. Data collection and data management were carried out on a nationwide basis and related to the histologic diagnosis [14]. We included all cases of tracheal cancer reported in the files of the NCR and found that four of 312 reported cases were misclassified (1.3%). In two other epidemiologic studies, the frequency of misclassification of tracheal tumors (16-29%) led to the conclusion that the incidence may be overestimated [1,5].

According to the study of Licht et al., tracheal cancer in Denmark makes up 0.02% of all reported malignancies; in our study, this proportion was higher (0.034%). This might indicate that some of the 308 cases of tracheal cancer that we found were misclassified. However, the data on all cases were extracted from the patients' medical records and checked individually by trained registration employees of the

Comprehensive Cancer Centers before being entered into the NCR [14]. For the coding of the data, national and international standards are used. Although registration errors will occur, it is unlikely that the difference between the results of Licht et al. and ours can be explained by misclassification.

Only a few other epidemiologic studies on tracheal cancer have been performed. In Finland, the annual incidence of tracheal cancer is 0.104 per 100,000 inhabitants, and the proportion of all malignancies accounted for by tracheal cancer (0.038%) [1]. This is in accordance with the figures in the Netherlands, which are 0.142 per 100,000 inhabitants and a proportion of 0.034% of all malignancies

Licht et al. in Denmark found that 17% of all cases of tracheal carcinoma were found incidentally at autopsy [5], whereas in our study this was only 4.9%. This is probably due to the difference in the total number of autopsies per year: in Denmark, autopsy is performed in 27% of all deaths [5], while in the Netherlands it is only performed in 7% [15].

Table 6. Treatment Modalities and Distribution of Histologic Types in 5 Epidemiologic Studies

Author	Year	Period	Type*	Cases	Histology (n)	Overall treatment† (n)
Licht**	2001	1978-1995	N	109	63% SCC (69) 7% ACC (8) 29% other (32)	7% surgery (6) 46% RT (42) 48% other†† (44)
Yang	1997	1979-1994	S	67	52% SCC (35) 8% ACC (5) 40% other (27)	18% surgery (12) 73% RT (49) 9% other (6)
Manninen	1993	1967-1985	N	95	72% SCC (68) 6% ACC (6) 22% other (21)	6% surgery (6) 63% RT (60) 31% other (29)
Gelder	1993	20 years	P	321	54% SCC (174) 11% ACC (34) 35% other (113)	10% surgery (31) 62% RT (199) 28% other (91)
Kurien	1981	1957-1974	R	97	46% SCC (45) 3% ACC (3) 51% other (49)	7% surgery (7) 27% RT (26) 66% other (64)
Present study**	2005	1989-2002	N	308	53% SCC (163) 7% ACC (22) 40% other (123)	12% surgery (34) 53% RT (156) 35% other (104)
Total				997	56% SCC (554) 8% ACC (78) 37% other (365)	10% surgery (96) 55% RT (532) 35% other (338)

* N = national registration, S = single institution, P = nationwide postal survey, R = regional registration

† Primary treatment is stated. Surgery includes cases with adjuvant radiotherapy. 'Other' therapy also includes none

** Cases found at autopsy were excluded from treatment analysis

†† Of which 24 patients underwent endoscopic local resection

When one looks at the available literature on the distribution of the histologic types of tracheal cancer (Table 6), it is striking that in all epidemiologic studies, including ours, SCC accounts for 46–72% of all cancers while ACC makes up only 3–11% [2,5-7,16]. In contrast, in studies performed in surgical clinics, ACC is seen in 30–50% of all cases [11,17-20]. In a study by Bhattacharyya, based on the U.S. SEER database, 19 of 92 cases of tracheal cancer consisted of ACC (20.7%). However, patients with distant metastasis were excluded in this study [21]. Gaissert suggests that this disparity in the distribution of histologic types of tracheal cancer could be explained by the absence of radiologic and pathologic review of cases in epidemiologic studies [17]. However, this is the third national epidemiologic study in which a lower percentage of ACC was found. All our cases were registered nationally only on the basis of a histologic diagnosis. Still, in all three of the national epidemiologic studies mentioned above, 47–80% of patients with ACC underwent surgical resection, while overall, only 6–18% received surgery. In a Danish national study, small cell and large cell carcinoma accounted for 7.3% and 1.8% of all cases respectively [5], while in our study these portions were 11.0% and 7.5% respectively. An explanation for these relatively high incidences could not be found, as pathology slides were not reviewed in this retrospective chart review. Gelder and Hetzel also observed an unexpected high incidence of small cell carcinoma (6%) [7].
In our patients, more than 50% of those with ACC received surgical treatment, compared to only 8.1% of the patients with other histologic types of primary tracheal carcinoma. More than 30% of all surgically treated patients had ACC. Moreover, it seems that patients with ACC are more often operable than patients with other histologic types [22]. These results are suggestive of a selection bias in studies from surgical clinics, as a result of which ACC appears to be a common histologic type.
It was already known that most patients with tracheal cancer are male [1,23]. ACC is associated with a more equal distribution between the sexes or may even be found predominantly in females [24]. Another characteristic of ACC is that it is found in younger patients. Gelder and Hetzel found a mean age of 50 years in 34 patients with ACC [7]. The 135 patients with ACC in the study of Gaissert et al. had a mean age of 49 years [9]. In our study, this difference in age was less clear and in fact not significant (p=0.054). The mean age of patients with ACC was almost 60 years (with an equal distribution between males and females). Patients with ACC have by far the best prognosis of all histological types, regardless of treatment modality [6,16,19], which is also confirmed by our series (Table 4). In our study, patients with ACC had a 10-year survival rate of 61%.

We also analyzed the impact of other primary tumors, prior to or after the diagnosis of tracheal cancer, on survival. However, no significant effect on survival was found. León et al. found that 16% of patients with malignancies of the head and neck developed other primary tumors, which led to a significant decrease in survival [25]. The high incidence of other primary tumors is closely related to the abuse of tobacco and alcohol [26]. It is known that the vast majority of patients with tracheal cancer are smokers. Of all patients with primary tracheal cancer, 77–86% smoke or have a

history of smoking [1,5,7]. This predominance is even more explicit in patients with SCC, of which 89–92% are smokers, whereas ACC is distributed more equally between non-smokers and smokers, the latter group making up 45–60% of all patients with ACC [7,9,27].

According to the studies listed in Table 6, 6–18% of all patients with tracheal cancer underwent surgery as their primary treatment, 27–73% were treated with radiotherapy and 9–66% had other types of treatment or best supportive care. These figures correspond to those for patients with tracheal cancer in the Netherlands during the period 1989–2002. When we look at the survival following different methods of treatment, it is clear that patients who underwent surgical resection of their tracheal cancer survived longer than patients who were treated otherwise ($p<0.0001$). One of the reasons for this difference is that ACC makes up 32.4% ($n=11$) of the group of operated patients ($n=34$). Nevertheless, when we looked at the patients with SCC separately, we found that in this histologically homogeneous group, patients treated with surgery had a 5-year survival of 41% compared to 11% in patients treated with radiotherapy ($p<0.0001$, Table 5). This indicates that, irrespective of histologic type, surgical treatment yields the best survival. The differences in outcome between surgery with and without adjuvant radiotherapy were not analyzed separately, since radiotherapy was used in patients selected by staging information and surgical margins. In a French multicenter study including 208 cases of tracheal tumors, Regnard et al. found that the 5-year survival rate after surgery was 62% [11]. However, this may be too optimistic, since 11% of the included tumors were benign. Gaissert et al. included 270 cases of tracheal cancer, half SCC and half ACC, and achieved a 5-year survival rate of 56% in operated cases [9]. A Japanese study even showed a 5-year survival rate of 72% in surgically treated patients, although this group consisted of only 16 patients, of which nine had SCC and seven had ACC [19]. Given these good results, the available literature on tracheal cancer shows consensus regarding treatment: surgery is the only realistic treatment with curative intent and leads to the best survival rates [18,28]. However, not all tumors in patients presenting with tracheal carcinoma are resectable due to locally advanced disease, metastatic disease or contraindicating co-morbidity [12,29].
Several other treatment modalities have been described. Endoscopic resection can be used to relieve airway obstruction but does not provide complete resection and the chances of a cure are therefore minimal [17]. Radiotherapy can also be used as palliation or as adjuvant treatment after surgery [30,31]. Webb et al. recommend adjuvant radiotherapy in patients treated with surgical excision [27]. Very poor survival rates in patients treated with radiotherapy alone are seen in most studies. A French study by Mornex et al. reported a 5-year survival rate of 8% in 82 patients treated with radiotherapy [8], and Makarewicz reported a 5-year survival rate of 9% in 23 cases in 1998 [32]. Our data show a 5-year survival rate of 11% in patients treated by primary radiotherapy. The application of endotracheal brachytherapy after external-beam irradiation has shown to improve local tumor control. This relatively new treatment modality is subject of future research to further optimize the management

of tracheal tumors. Cisplatinum based chemotherapy is the treatment of choice for selected patients with disseminated and locally advanced disease. The intent of chemotherapy is usually palliative and chemotherapy can only be advised in patients with a good performance status. Small cell cancer of the trachea is very rare and is often part of a disseminated disease where chemotherapy can be successful but no large trials have been published [33] There is very little data available on the effect of adjuvant or neoadjuvant chemotherapy or concurrent chemoradiotherapy of non small cell tracheal carcinomas [34].

It can be expected that only patients in the best clinical condition and with the most favorable tumor stage are offered surgery, thus affecting the survival rate. Still, Gaissert [17] and Macchiarini [12] state that, unless technically impossible, surgery should be the treatment of choice in patients with tracheal cancer. The implementation of this recommendation is impeded by the lack of a uniform staging system for tracheal cancer, because the classic TNM-staging cannot be applied. New staging systems for tracheal carcinomas have been suggested by Bhattacharyya [21] and Macchiarini [12]. The value of these systems should be subject of future research projects.

Hazama et al. and Gaissert concluded that resection is indicated in even more than 50% of all patients with tracheal cancer [17,20]. This is in contrast to all the studies listed in Table 6, including our study, in which only 10% were treated surgically. The reason why surgery is considered in only a few cases may be that only few centers have gained experience in the management of tracheal malignancies because of their rarity [17]. This is also supported by Gelder and Hetzel [7]. Licht et al. also report a nihilistic attitude towards the management of tracheal cancer in Denmark [5]. Based on our findings, this also seems to be the case in the Netherlands, although future research is needed to determine to what extent contra-indications to surgery play a role in the low amount of patients treated with surgical resection of their tracheal cancer.

Conclusion

Looking at the survival rates in our study, we can conclude that overall, the prognosis of patients with tracheal cancer is dismal. Surgery of patients with a tracheal carcinoma can lead to a significantly better survival, compared to radiotherapy. In our patients and in other epidemiologic studies, however, surgery was offered to only 10% of all patients. Several studies indicate that surgery would be applicable in at least 50% of all cases of tracheal cancer. Whether this discrepancy is based on a difference in patient population or unawareness among physicians about developing treatment possibilities needs to be investigated.
Research should be conducted to develop a standard classification that can be used to determine resectability. Given the infrequent incidence of this disease, the management and treatment of these patients should be performed by

multidisciplinary teams in centers equipped and experienced with the full range of treatment modalities (surgery, radiotherapy, chemotherapy and endobronchial treatment) in order to achieve more experience with this rare tumor within these teams. We believe that this centralization could lead to better palliative care and may improve survival in selected patients. Further studies are needed to evaluate the role of adjuvant chemotherapy and concurrent or sequential chemoradiotherapy to further improve survival.

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CHAPTER FOUR

4.2 – Undertreatment of Tracheal Carcinoma: Multidisciplinary Audit of Epidemiologic Data

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ABSTRACT

Background: National epidemiologic data were examined to determine the eligibility for curative therapy in tracheal carcinoma.

Methods: An expert audit of primary tracheal carcinomas registered from 2000 to 2005 with the Netherlands Cancer Registry (NCR) included blinded patient data and radiographic review to assess diagnosis and resectability. Actual treatment was compared to the opinions of a multidisciplinary panel (Radboud panel) and a second reviewer.

Results: Of 101 NCR-registered primary tracheal carcinomas, the Radboud panel diagnosis was metastatic disease or local extension of adjacent tumors in 34. Seventeen cases were excluded for missing data. In 50 cases confirmed by panel and second reviewer, actual treatment consisted of surgery in 24% (12/50), radiotherapy in 58% (29/50), endobronchial treatment in 12% (6/50), and observation in 6% (3/50). Both panel and second reviewer identified 16 additional surgical candidates, a total of 56% (28/50). Treatment recommendations of panel and second reviewer disagreed in 4 cases (8%).

Conclusions: One third of NCR-registered primary tracheal carcinomas were misclassified non-tracheal primaries involving the trachea. A majority of cases meeting audit criteria for diagnosis and surgical resection was treated with other modalities. Inter-reviewer disagreement was small. The audit of a national cancer registry suggests that incorrect diagnosis and undertreatment are common in rare airway tumors.

Introduction

Primary malignancies of the trachea are rare and challenging tumors. Surgical resection of the involved tracheal segment is the treatment of choice [1] and long-term disease-free survival have been reported following tracheal resection [2,3]. At least half of all patients with primary tracheal carcinoma are surgical candidates according to clinical series [4,5]. The actual treatment of tracheal cancer in the Netherlands as reported for the period 1989 to 2002 consisted of resection in only 12% of cases [6]. Identical proportions were found in epidemiologic studies from Denmark and Finland [7,8]. The discrepancy between reported ratios of surgical clinics and these epidemiologic studies may be in part based on patient selection. However, some authors suspected a lack of knowledge and a nihilistic attitude towards the treatment of tracheal malignancies [7,8].
Previous epidemiologic studies contained database information [7], but no systematic review of radiographs, to explain the discrepancy between clinical and epidemiologic data. To determine the proportion of the Dutch cancer registry cases of tracheal cancer whose radiographic findings are consistent with the diagnosis and who are candidates for surgical resection, a nationwide audit of cases was conducted.

Methods and Materials

Patient Selection
In a six-year period from 2000 to 2005, all cases coded for primary tracheal carcinoma, labeled C33.9 according to the International Classification of Diseases for Oncology, 3rd Revision (ICD-O-3) [9] and reported to the Netherlands Cancer Registry (NCR), through all nine regional cancer registries, were selected. The main source of notification is the national archive of pathology reports (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief, PALGA), complemented by data from the national hospital discharge registry with case summaries of all patients. The documentation of registered tumors is completed by reviewers at the regional registries who excerpt patient hospital charts. We received permission for this study from the national supervisory committee of the NCR. A waiver for patient consent was obtained with the provision that the primary care physician would agree to enrolment in the study.

Patient Data Collection
From the database of the NCR, name and address of the primary care physician concerning each patient were acquired. All physicians gave permission to include their patients into the study following a written request. Copies of patient charts detailing diagnosis and treatment of tracheal disease were gathered with additional documentation from referring physicians or specialists providing second opinions. Information on patient and clinical characteristics, diagnostic procedures, tumor pathology, and treatment were entered into a study database. The interval from first presentation to a specialist until a histologic diagnosis was obtained and termed

diagnostic delay. Patient charts were searched for documentation of therapeutic decisions and potential contra-indications to surgical treatment. Thoracic or otolaryngologic consultation, where documented, was recorded. To protect confidentiality, data entered the audit anonymised and panel members or second reviewer had no access to patient records or identifiers.

The minimum diagnostic evaluation that was considered complete consisted of cross-sectional imaging by computed tomography (CT) or magnetic resonance imaging (MRI) and bronchoscopy. Cases were excluded if documentation of evaluation was unavailable or abnormal findings of either diagnostic modality were not explained or evaluated. Diagnostic images were obtained from radiological hospital archives for each case. From these images, tumor length and extension to other organs, lymph node enlargement, presence of metastatic disease, and evidence of potential comorbid conditions were recorded. Where radiological tumor length diverged from bronchoscopic descriptions, the longer length was recorded. Evaluation of liver and adrenal glands was assumed when a dedicated abdominal CT was obtained or both organs were shown on the chest study.

Audit Case Review

Cases were reviewed by a multidisciplinary panel of physicians treating tracheal cancer at Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands (Radboud panel). The panel consisted of one pulmonary physician (HH), one cardiothoracic surgeon (AV), one radiologist (LD), two radiation oncologists (JK and JB), and one surgical head & neck oncologist (HM). A second review, independent from the Radboud panel, was provided by a thoracic surgeon with experience in tracheal carcinoma (HG).

For each case, clinical summaries in combination with CT or MRI of the trachea and chest were reviewed. Auditors were given demographic and historic information including sex, age, co-morbidity, prior malignancy and treatment, complaints, and excerpts of available radiographic, endoscopic, pathology or staging reports. The team was blinded to the actual treatment.

Audit of the Diagnosis of Primary Tracheal Carcinoma

The audit consisted of two parts, both done by the Radboud panel and second reviewer. The first part reviewed the primary diagnosis. In the presence of enlarged mediastinal lymph nodes, the tumor was assumed to be primary tracheal carcinoma only when the main tumor mass was located in the trachea, the tracheal tumor was separate from mediastinal lymph nodes and no other radiographic finding indicated the presence of a primary carcinoma of the lung elsewhere. If the main tumor mass was centered either in a mainstem bronchus or in a different organ adjacent to the trachea, in the esophagus or the larynx, the tumor was assumed to be a local extension and not primary tracheal carcinoma.

Audit of Treatment

For the second part of the audit, Radboud panel and second reviewer determined resectability and therapeutic options in each case. Tumors were assumed to be resectable when the tumor-bearing tracheal segment could be removed and reconstructed by primary anastomosis, taking into account age and body habitus of the patient (between 20 and 50% of the total tracheal length), absence of vital organ invasion such as the heart or great vessels and of mediastinal lymph node involvement. Previous high dose (>50 Gy) irradiation to the trachea was also regarded as a contraindication to resection.

Radboud panel findings regarding resectability and advised management were consensus-based, replicating every-day multidisciplinary oncology practice. The opinion of the second reviewer was compared with the panel assessment. The combined opinion of panel and second reviewer was compared with actual treatment, marking cases as surgical candidates only when decided independently by both reviews.

Statistical Analysis

Statistical testing was performed with SPSS 14.0 statistical software program (SPSS Inc, Chicago, IL). Continuous variables were compared with the One-Way ANOVA test and categorical variables were compared with the Chi-Square test.

Results

The Diagnosis of Tracheal Cancer

The results from the audit process are depicted in Figure 1. Excluding two cases in children and two found at autopsy, the NCR identified 104 tracheal carcinomas from 51 hospitals in the period 2000 - 2005. Three cases for which imaging studies could not be located were excluded from analysis.

Of 101 cases reviewed in the initial audit, 34 carcinomas (33.7%) were judged to originate from sites other than the trachea and excluded from further analysis. In 19.8% (20/101), a tracheal biopsy positive for carcinoma originated from a primary tumor elsewhere: the lung or mainstem bronchus with ingrowth into trachea in 14 cases (squamous cell carcinoma (SCC) in 7, small cell carcinoma in 3, large cell carcinoma in 3, and adenocarcinoma in 1), the esophagus in 3 (all SCC), and the larynx in 3 (SCC in 2 and carcinoma in situ in 1). One of these laryngeal tumors had been surgically resected.

In the other 13.9% (14/101), mediastinal lymphadenopathy extended into the tracheal lumen or caused malignant stricture without detectable primary tumor. These cases were regarded as a metastatic malignant stricture.

Missing Information

Seventeen cases, none resected, were excluded due to insufficient clinical information. There was no staging for distant metastasis in 7 cases: in 3, the chest CT was incomplete and in 4, potential metastasis identified by CT was not evaluated.

Table 1. Patient Characteristics and Referral Pattern

	n	%		n	%
Sex			Referred to		
Male	30	60	Pulmonologist	44	88
Female	20	40	Internist	3	6
			Otolaryngologist	2	4
Co-morbidities			Cardiologist	1	2
Alcohol use	15	30			
Cardiovascular	10	20	Symptoms		
COPD	8	16	Dyspnea	33	66
Hypertension	5	10	Cough	28	56
Diabetes	5	10	Hemoptysis	21	42
Prior stroke	2	4	Stridor	18	36
Pulmonary embolus	2	4	Weight loss	6	12
Deep vein thrombosis	1	2	Hoarseness	4	8
Asthma	1	2	Dysphagia	3	6
Obesity	1	2	Neck mass	3	6
Benign tracheal stenosis	1	2	Chest pain	2	4
Other	8	16	Fatigue	2	4
None	19	38	Other	3	6
			None	1	2
Smoking history					
Yes	37	74	Duration of symptoms*		
No	7	14	< 1 week	2	4
Unknown	6	12	1 - 4 weeks	15	31
			1 - 3 months	17	35
Prior airway cancer			3 - 6 months	9	18
Lung	11	22	6 - 12 months	2	4
Larynx	3	6	> 12 months	4	8
Oropharynx	1	2			
			Prior diagnosis*		
Prior cancer, non-airway			Bronchitis	7	14
Colon	3	6	Asthma	4	8
Prostate	1	2	Other	3	6
Breast	1	2	None	36	73
Thyroid	1	2			
Uterine	1	2			

* In 49 patients presenting with symptoms

Resectability could not be determined in 6 cases. Extent and length of an adenoid cystic carcinoma (ACC) was unclear in 2, and in the other cases bronchoscopy was not done or not documented, the extent of esophageal invasion was not evaluated, or enlarged mediastinal lymph nodes were not biopsied.
Operability was uncertain due to important cardiovascular disease in 2 cases and locally advanced synchronous bronchial carcinoma in 2 others.

Patient Characteristics and Presentation
Characteristics of the remaining 50 cases are shown in Table 1. Mean age was 63.7 years (range 32 – 85 years). Two of 15 prior airway cancers were synchronous

bronchial cancer. Two other cases had synchronous colon carcinoma and papillary thyroid carcinoma, respectively.
Cases of ACC were younger (mean 57.9 years versus 66.4 years, $p = 0.047$), more often female (61.5% versus 37.0%, NS), less often smokers (58.3% versus 91.7%, $p = 0.017$) and had fewer prior airway malignancies (0% versus 48.1%, $p = 0.002$) than those with SCC.

The four most common presenting symptoms were dyspnea, cough, hemoptysis, and stridor. In 94.0% (47/50), one or more, and in 72% (36/50), two or more of these symptoms were present. One tracheal carcinoma presented asymptomatic concomitant with bronchial cancer during workup of a nasal inverted papilloma. Ten cases were first seen at a tertiary centre. Referral to tertiary centres occurred in 9 cases for treatment and in 18 for a second opinion, while 13 (26%) were not referred. Diagnostic delay measured 9 days (mean 24) and ranged from 0 to 285 days.

Diagnostic Procedures
Diagnostic tests and tumor histology are summarized in Tables 2 and 3. Endoscopic tumor and tracheal length was measured by the treating physician in 28% of cases (14/50). In six cases, cervical nodal invasion was found on CT and confirmed with biopsy. In five cases (10%), chest CT showed pulmonary metastases. Abdominal CT showed liver metastases in 1 case.

Table 2. Diagnostics and Dissemination Tests

	n	%		n	%
Seen on chest X-ray			Localization		
Yes	14	28	Proximal	19	38
No	36	72	Middle	11	22
			Distal	20	40
Seen on chest / neck CT					
Yes	42	84	Dissemination tests		
No	8	16	CT liver and adrenal glands	29	58
			PET scan	14	28
Endoscopic examination			Scintigraphy	6	12
Flexible	17	34	Esophagoscopy	6	12
Rigid	5	10	US abdomen	5	10
Both flexible and rigid	28	56	Histology neck node	5	10
			MRI of the chest	4	8
Seen at endoscopy			US neck	4	8
Yes	50	100	CT or MRI brain	3	6
No	0	0	Endoesophageal US	3	6
			Medistinoscopy	2	4
			High resolution chest CT	2	4
			Swallow X-ray	1	2

CT = computed tomography, PET = positron emission tomography, US = ultrasound, MRI = magnetic resonance imaging

Table 3. Histologic Types Found in 50 Cases of Primary Tracheal Carcinoma

	n	%
Squamous cell carcinoma	27	54
Adenoid cystic carcinoma	13	26
Carcinoid	4	8
Large cell carcinoma	3	6
Adenocarcinoma	2	4
Small cell carcinoma	1	2

Actual Treatment

Primary treatment was radiotherapy in 58% (29/50) of cases, combined with endobronchial treatment in 8, chemotherapy in 3 and both endobronchial treatment and chemotherapy in 5. The radiation dose was less than 39 Gy in 6, between 39 and 59 Gy in 4, above 59 Gy in 19 cases, and 70 Gy or more in 6 of these cases. Surgical resection was performed in 24% (12/50). Resection was preceded by endoscopic debulking in 4 cases. Postoperative adjuvant radiotherapy was administered using a dose of 39 to 59 Gy in 4 cases and more than 59 Gy in 5. In 12% of cases (6/50), primary treatment consisted of endobronchial resection. In 6% of cases (3/50), only supportive care had been administered. Seven of 13 ACC cases underwent surgical airway resection (54%).

Radboud Panel Opinion

In 10 cases without distant metastases, the tracheal tumor was considered unresectable due to mediastinal invasion in 5, excessive length in 4, and dissemination during previous thyroidectomy in 1. The panel regarded 3 cases resectable but inoperable due to advanced age or local recurrence of a peripheral lung cancer. In 31 of 50 primary tracheal carcinoma (62%), the panel advised surgical tracheal resection with curative intent.

Opinion of Second Reviewer

In 4 of 50 cases (8%), the individual thoracic surgeon differed from the panel regarding tumor resectability. The second reviewer judged 3 cases considered resectable by the panel as unresectable because of prior cervicomediastinal radiation. The Radboud panel considered 1 case judged resectable by the second reviewer as unresectable due to lymphadenopathy. Thus, there were 28 candidates for resection as determined by both Radboud panel and second reviewer.

Potential Surgical Candidates

Of 28 potential surgical candidates, actual treatment in 16 cases (57%) consisted of other modalities: radiotherapy in 11, endobronchial therapy in 4, and supportive care in 1. Only 43% (12/28) of surgical candidates actually underwent surgical resection. Age, histologic types and tumor length in these groups are shown in Table 4. Contraindications to surgery as stated in the medical chart are listed in Table 5.

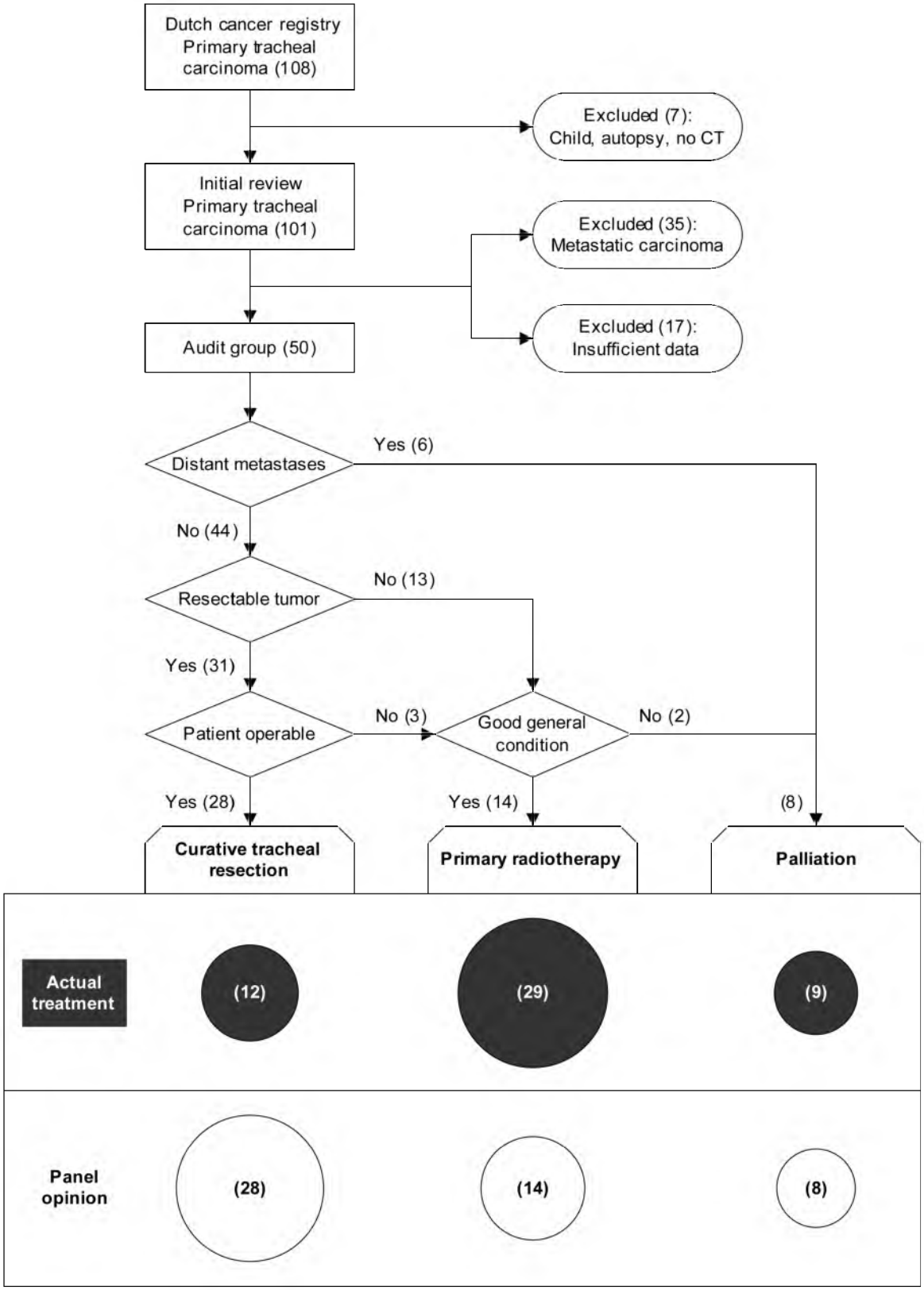

Figure 1. Patient is noted as resectable only when indicated by both the review by the Radboud panel and the second reviewer. The actual treatment (dark balloons) is compared with the assessment of the audit (white balloons) in 50 patients with primary tracheal carcinoma (p = 0.005). Surface area of balloons represents the number of patients in each group.

Table 4. Patient and Tumor Characteristics in Surgical and Non-Surgical Candidates

	N	Mean age in years (range)	Histologic type (%)				Mean tumor length in cm (range)
			SCC	ACC	Cd	Other	
Surgical candidates	28	61.4[a] (32 - 80)	32.1	35.7	14.3	17.9	3.0[b] (1.0 - 5.5)
Resected	12	57.8[c] (37 - 75)	33.3	58.3	8.3	0	2.8[d] (1.5 - 5.5)
Not resected	16	64.3[c] (32 - 80)	31.3	18.8	18.8	31.3	3.3[d] (1.0 - 5.2)
Non-surgical candidates	22	66.5[a] (46 - 85)	81.8	13.6	0	4.5	5.5[b] (1.4 - 12.0)
Overall	50	63.7 (32 - 85)	54.0	26.0	8.0	12.0	4.2 (1.0 - 12.0)

SCC = squamous cell carcinoma, ACC = adenoid cystic carcinoma, Cd = carcinoid
[a] *P*-value 0.165
[b] *P*-value < 0.0001
[c] *P*-value 0.190
[d] *P*-value 0.358

Surgical consultation had been obtained in half (8/16) of surgical candidates who had not undergone resection.
If we assume that none of the 17 cases excluded from review due to insufficient clinical information would have been a candidate for tracheal resection, 42% (28/67) of cases would have been surgical candidates, as opposed to the actual resection rate of 18% (12/67; $p = 0.003$).

Table 5. Documented Reasons for Non-Surgical Management in 16 Non-Resected Surgical Candidates

	n	%
Tracheal process unresectable	7	43.8
Segment too long	2	12.5
Possible ingrowth muscular esophagus	1	6.3
Long dysplastic area in trachea	1	6.3
Not documented	1	6.3
Carcinoid tumor	3	18.8
Patient's preference	1	6.3
Not documented	7	43.8

Discussion

An audit review of the NCR finds metastases to the trachea in one third of cases registered, and therefore in our view misclassified, as primary tracheal carcinoma. Our study further finds that less than half of all cases with resectable tumors undergo surgical resection. These findings highlight the limited validity of epidemiologic data for this and other rare diseases that are reported to the registry without radiologic or histologic review. The audit more importantly points to problems in the clinical care of patients with uncommon tracheal tumors.
The concept of unsolicited panel and radiographic review of all registered cases of a certain type of tumor in one country in a designated period, is unique in its design, and, to our best knowledge, never described before. While external auditing of blinded and abstracted data by a panel of experts itself is subject to limitations, this method approximates the concept of multidisciplinary oncologic review by local experts adopted for common tumors in every-day practice. Treatment advice of our panel review is furthermore reproducible, as the inter-reviewer disagreement between the Radboud panel and a second reviewer was small (8%). In rare diseases such as tracheal tumors, however, the pool of experts is small and often not local. The emphasis on local surgical assessment and care may imply a potentially profound difference in the indications for surgical therapy and the outcome of individual patients.

The high proportion of misclassified tracheal carcinomas in the NCR suggests that the registration process for uncommon tumors may be improved. Errors in this classification consisted of a misattribution of tumors originating from adjacent organs or mediastinal lymphadenopathy with invasion of the airway wall to the trachea. Any biopsy of tumor from the trachea is reported to the NCR as tracheal cancer through the direct link with the national pathology database (PALGA). The final registration in the NCR database, however, involves a review of the patient medical chart. Some of the misdiagnoses may therefore have occurred when the tumor site of origin was misclassified in the report to the NCR. A retrospective review may correct the database error, but not the implications for patient care.
Three other epidemiologic studies of national cancer registry data also found misclassified tracheal carcinomas. A Finnish study found 36 metastatic tracheal lesions among 133 registered primary carcinomas (27.1%) [10], while a Danish audit excluded 16 misclassified tumors from 130 registered cases (12.3%) [7]. In a review of the American Surveillance, Epidemiology, and End Results (SEER) database, Bhattacharyya disregarded cases with distant metastasis and excluded an additional 7 of 99 cases (7.1%) with carcinoma in situ or unclear pathology [11]. None of these studies, however, included a complete radiological review and thus may have underestimated the proportion of misclassified metastatic tumors. Misclassification, conversely, could also have occurred by labeling cases of primary tracheal cancer as metastatic bronchial, laryngeal, esophageal or thyroidal carcinoma. This error, however, is expected to occur less frequently since the registry is linked to the site of

biopsy requiring active intervention by the responsible physician to change the tumor site.

A critical assessment of our previous study on incidence and treatment of tracheal carcinoma, also based on the files of the NCR but without review of radiographs [6], now suggests that the incidence of this disease in the Netherlands is overestimated and probably closer to 0.1 in every 100.000 persons per year. The high rate of small cell carcinoma in our previous study (11.0%), regarded as a marker of contamination with metastatic disease [12], was likely caused by the misclassification of peripheral bronchial carcinomas. We estimate that ACC accounts for approximately one quarter of tracheal cancers. In surgical series, ACC is encountered in 40 – 60% of cases [13-15]. The reported incidence of SCC lies fairly constant around 50% in both epidemiologic and surgical series [3,6,16-18]. Future epidemiologic studies of tracheal carcinoma and other tumors of low incidence should therefore include an audit review of radiographic and, where feasible, also histologic images.

Our study had important limitations. A retrospective case review does not include patient contact, physical assessment, or endoscopic examination. The locoregional extent of disease, in the context of patient factors such as age, weight, and neck mobility, is the single most important factor determining resectability [2]. Despite panel review of CT's, endoscopy reports were usually brief and often non-descriptive. Endoscopic measurements of tracheal and tumor length were missing in 72% of patients. Thus, the actual resectability rate may be lower than our estimate. Still, tumor length in potential surgical candidates was well within the range of resectable disease [2] and differences of mean and range of tumor length between cases treated with resection and additional surgical candidates were small (mean 2.8 and 3.3 cm, respectively). A further potential source of error in our study was the determination of operability status based on available evidence in the patient's medical chart. However, the Radboud panel excluded 4 cases in which the absence or presence of medical contra-indications to surgery could not be determined, even though patients are rarely declared unresectable due to medical contraindications [2]. As depicted in Table 5, no medical contraindications were identified in any of the 16 additional surgical candidates who did not undergo surgical resection.

Our results provide additional evidence that half of all patients with primary tracheal cancer are surgical candidates [4,5]. The balance is tipped furthest toward resection in ACC: the Radboud panel judged 10 of 13 cases (77%) to have resectable disease. As this national audit was preceded by epidemiologic studies in Denmark, Finland and the United Kingdom with comparable outcome with those in the Netherlands, these results are likely representative for the situation in most western European countries [6-8,16].
We believe that each patient diagnosed with a tracheal tumor should be referred to a tertiary oncology centre with multidisciplinary experience in the treatment of tracheal tumors. Given the rarity of the disease, to warrant sufficient exposure to malignant

tracheal pathology and to maintain experience, one centre per each population of an estimated 10 - 20 million would be optimal. In the Dutch situation, this would mean one national centre. By centralizing the care for patients with this rare airway tumor, more patients may be selected for surgical resection, thus potentially improving outcome. As this improvement is inferred but untested, close evaluation would be needed once a centralized system is implemented to assess the exact benefit of this new strategy.

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CHAPTER FIVE

5.1 – The Management of Thyroid Carcinoma Invading the Larynx or Trachea

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ABSTRACT

Objective: To describe the controversies in the management of thyroid carcinoma invading the airway.

Study design: contemporary review of literature, level of evidence: 5.

Results: Invasion of the larynx or trachea by thyroid carcinoma is uncommon and often identified at the time of operation, when the surgeon must decide the extent of resection. Invasion of the airway is associated with loss of tumor differentiation and a reduction in long-term survival compared to tumors limited to the thyroid gland. Whether or not the invaded airway should be resected remains controversial. Tangential shave excision of tumor is commonly performed, despite a marked risk of local recurrence. Circumferential sleeve resection of the larynx and trachea is safe and lowers the risk of local recurrence. In recurrent disease, laryngotracheal resection provides effective palliation of airway obstruction and hemoptysis.

Conclusion: Long-term (>10-20 years) prospective studies are required to compare the outcome after shave excision with segmental airway resection for thyroid carcinoma. Based on the current literature and on our experience, we advocate circumferential tracheal resection in the setting of airway involvement.

Introduction

Invasion of the larynx or trachea by thyroid cancer ranges from asymptomatic tracheal adherence to airway obstruction or bleeding from transmural invasion. Over half of all deaths from well- and poorly differentiated thyroid cancer are due to airway obstruction and bleeding [1], but death in thyroid cancer remains uncommon. Tracheal invasion by tumor is associated with loss of cellular differentiation and a reduction of long-term survival compared to tumors limited to the thyroid gland. Usually identified at the time of operation, airway invasion demands from the surgeon a decision on the extent of resection. Tracheal invasion at the time of thyroidectomy is often treated with tangential "shave" resection; the margins are difficult if not impossible to assess. Complete resection of local disease is assumed to be a prime objective in the surgical treatment of thyroid carcinoma, producing the best palliation and longest survival. A meta-analysis of all available surgical techniques is desirable but presently unachievable. The diversity of the reported experience with regards to primary and recurrent disease, degree of tumor differentiation, laryngeal or tracheal invasion, present or absent lymph node involvement, and type of resection, has not been summarized in a statistically meaningful manner. Kim and associates provided a careful tabulation of respiratory tract invasion in their review, but no statistical analysis [2]. Any conclusions or recommendations regarding the extent of resection in patients with thyroid carcinoma invading the airway rest therefore on incomplete data The purpose of this review is to describe the clinical presentation and long-term outcome of laryngotracheal invasion, the methods of resection, and the clinical data supporting their use.

Incidence of Laryngotracheal Invasion

The argument for conservative surgical therapy of laryngotracheal invasion is based on the excellent prognosis of well-differentiated tumors of papillary and follicular histology, with over 90% of patients surviving 10 years after complete resection [3,4].
The proportion of patients with thyroid cancer involving the larynx and trachea depends on histology, disease severity, and the definition of invasion. Extrathyroidal invasion into the trachea or larynx was noted in 3.6% [5] to 22.9% [6] of all patients undergoing thyroidectomy, with the highest proportion in a tertiary referral center. Luminal tumor inside the trachea, the most advanced stage of invasion, was visible on endoscopy in only 0.5 to 1.5% of patients presenting for resection [7-9]. The surgeon's definition of invasion, ranging from any attachment of the gland to gross tumor transgression further influences this proportion. Tracheal or esophageal adherence was noted in 10.9% (45/412) of patients in a referral center [10], while Clark and associates found deep laryngeal invasion necessitating laryngectomy in 5 of 218 (2.3%) patients undergoing thyroidectomy [11].

Table 1. Occurrence of Laryngotracheal Invasion by Thyroid Carcinoma (Studies >50 Cases)

Author	Year	Period (years)	No. of Thyroid Carcinomas (N)	Airway Involvement		Well Differentiated (%)
				No.	%	
All thyroid carcinomas						
Schindel, J [15]	1971	15	225	10	4.4	ns
Breaux, GP [16]	1980	10	210	44	21.0	72.2
Segal, K [17]	1984	25	500	29	5.8	65.5
Tsumori, T [18]	1985	24	180	28	15.6	ns
McCarty, TM [19]	1997	44	597	40	6.7	85
Koike, E [20]	2001	0.5	171	16	9.4	93.8
Sywak, M [21]	2003	2	97	7	7.2	100
Tsai, YF [22]	2005	15	532	43	8.1	93.0
Randolph, GW [23]	2006	-	135	21	15.6	ns
Well-differentiated thyroid carcinomas						
Friedman, M [24]	1982	30	190	13	6.8	100
McConahey, WM [12]	1986	25	859	85	9.9	100
Nishida, T [6]	1997	25	301	69	22.9	100
Hu, A [14]	2007	38	576	13	2.3	100
Laryngectomy						
Clark, RL [11]	1966	19	218	5	2.3	ns
Radiologic evidence						
Lawson, VG† [13]	1983	-	100	35	35.0	ns
Invasion of aerodigestive tract						
Melliere, DJ [10]	1993	20	412	45	10.9	64.4
Ballantyne, AJ [25]	1994	40	1098	46	4.2	65.2
Segal, K [26]	2006	40	1200	49	4.1	100
Tracheal cartilage invasion only						
Park, CS [5]	1993	10	432	16	3.7	100
Tracheal luminal disease						
Frazell, EL [9]	1958	25	393	6	1.5	100
Britto, E [7]	1990	20	1925	10	0.5	100
Total			10251	595	5.8	

† The Cases Reported by Lawson are not Included in the Totals

ns = not stated

Two retrospective studies from the same institution noted widely different results depending on whether endoluminal disease (0.9% in 2000 patients [8]) or external adherence to the wall (9.9% in 859 patients [12]) determined invasion. Radiologic criteria such as compression or displacement by tumor, found in up to 35%, probably overestimate invasion [13]. A recent study from Hu and colleagues reported macroscopic tracheal invasion in 13 of 531 patients (2.4%) with more than five years of follow-up [14]. In a total of 20 studies (Table 1) [5-7,9-26], we found 10251 patients with

thyroid cancer 595 (5.8%) of whom had airway invasion. In the absence of epidemiologic studies, this may be the best general estimate of laryngotracheal tumor adherence or invasion among all patients presenting for surgical resection.

Tumor Characteristics and Prognosis

Tracheal invasion is of interest to surgeons because it is a marker for more aggressive tumors and defines a patient population at greater risk of death from what is otherwise a comparably indolent tumor. Indeed, malignant airway obstruction from either a primary tumor or recurrent disease is the cause of death in half of all patients with thyroid carcinoma [1]. Active local disease is further stated to be present in greater than 80% of patients who die of thyroid carcinoma [27]. Among 18 cases of thyroid cancer infiltrating the trachea, Tsumori and associates found poor differentiation in 50% of papillary and follicular carcinoma compared to 11.4% when airway was not invaded [18]. Within individual tumors, Tsumori found loss of differentiation along the axis from well-differentiated center of the gland to the poorly differentiated site of airway invasion, suggesting that invasion beyond the capsule and loss of differentiation are related phenomena. Depth of invasion appears to predict outcome, with shorter survival in patients with endoluminal tumor, as shown by Shin and colleagues [28]. In Djalilian and associates' study of 18 patients with intraluminal thyroid cancer, for example, 11 patients died of disease, 3 were alive with metastasis, and the longest survivor had lung metastasis 8 years after laryngectomy [8]. Ten of these patients had thyroidectomy and 10 either laryngectomy or tracheal resection. Furthermore, among 292 patients with well-differentiated papillary carcinoma, the most commonly encountered histology and hence the group of greatest interest, Czaja and McCaffrey identified laryngotracheal invasion in 124 patients (41%) as a significant independent predictor of death [29]. In separate studies, both McCaffrey [30] and Ito and their associates [31] found that aerodigestive tract invasion was an important negative prognostic factor. These data indicate that tracheal invasion lowers long-term survival.

Presentation of Laryngotracheal Invasion

Symptoms underestimate the depth of airway invasion. The symptoms associated with mucosal penetration, bleeding and airway obstruction, define a small subset of patients with the most advanced degree of invasion. Even deep tumor invasion into the tracheal wall is often not identified before operation unless fixation of the gland is obvious on physical examination. Among 40 patients with gross airway invasion, McCarty reported hoarseness in 22%, hemoptysis in 11% and dyspnea in 5% [19]. In surgical series of tracheal resection for patients with tumors invading the trachea, both airway obstruction and bleeding are more common.

We noted dyspnea in 31% and hemoptysis in 24%, while 10% had no symptoms [32]. Tsumori and colleagues found hemoptysis in 39% and some degree of dyspnea in 89% of 18 patients [18]. Hemoptysis occurred in 19 of 24 patients (79%) in a study by Ishihara and associates [1].

Diagnosis of Laryngotracheal Invasion

The preoperative diagnosis of tracheal invasion is unusual. McCarty and associates identified laryngotracheal invasion in 83% of their patients during the operation [19].

Ultrasonography

Ultrasound may identify patients with local invasion. In papillary carcinoma, the sensitivity of preoperative ultrasound for tracheal invasion was 42.9% and for esophageal invasion 28.6% [33]. Ultrasound in 24 patients correctly predicted invasion of the tracheal adventitia in 2 of 4, the intercartilage space in 9 of 10, and the mucosa in 9 of 10 patients [34]. Invasion was thus correctly identified before exploration in 83% (20/24), higher than in the earlier study and coincidentally the inverse of McCarty's findings. Tomoda and colleagues found histologically confirmed ultrasonographic evidence of airway invasion in 11 of 13 tumors (85%) and false-positive findings in 32 of 496 patients (6.5%) [35]. In experienced hands, cervical ultrasound may therefore allow accurate preoperative prediction of airway invasion.

Bronchoscopy

Bronchoscopic examination identifies luminal compression, erythema and edema, neovascular formation, and frank mucosal invasion (Shin stage IV). Flexible endoscopes have a lower optic resolution than rigid systems and observe the mucosa at an angle, not head-on. Rigid bronchoscopy conducted in the fully anesthetized patient affords undisturbed and unhurried inspection at telescope angles from 0 to 90 degrees. Koike and colleagues reported 16 patients with airway invasion who underwent preoperative flexible bronchoscopy [20]. They graded a negative bronchoscopic examination as diagnostic of perichondrial invasion only (Shin stage I), treating 4 such patients with shaving of the tracheal wall alone, although Shin and associates specifically described normal bronchoscopic findings in stages 0 through III [28]. Koike treated deeper invasion associated with at least one abnormal bronchoscopic characteristic with full thickness resection. Randolph and Kamani advocate, and we support, the use of pre-operative endoscopy in all patients undergoing thyroidectomy to diagnose vocal cord paralysis and invasive thyroid disease [23]. The purpose of endoscopic examination is not to identify patients who may undergo shave resection, but to diagnose advanced invasion and estimate luminal extent and resectability.

Staging of Laryngotracheal Invasion

A staging system for local laryngotracheal invasion evolved from investigating the lymphatic drainage of the laryngotracheal unit and the thyroid gland [28]. Shin and associates found a relationship between the depth of invasion and intermediate-term (5-year) survival in 22 patients with papillary carcinoma and airway invasion [28]. Table 2 details the five stages of this system. An important corollary of the Shin staging was the likelihood of positive resection margins and lymph node involvement, present in 54 and 91%, respectively, of patients with the most advanced stage IV, compared to 36 and 36%, respectively, in stages I to III. The Shin staging requires a full thickness specimen of tracheal or laryngeal wall to precisely determine depth of invasion. This system is therefore misinterpreted when applied to patients undergoing shave resection [6,20]. The purpose of staging organ invasion in this manner lies in the clinical observation that tumor depth and prognosis are related.

Table 2. Staging for Differentiated Thyroid Carcinoma Based on the Extent of Tracheal Invasion According to Shin et al. [28]

Stages	Definition
Stage 0	Carcinoma confined to the substance of the thyroid
Stage I	Extension through the capsule of the thyroid gland and abutting the external perichondrium
Stage II	Invasion between the rings of cartilage or destroying the cartilage
Stage III	Extension through the cartilage or between the cartolaginous plates into the lamina propria of the tracheal mucosa
Stage IV	Extension through the entire thickness of and expansion into the tracheal mucosa

Other staging schemes for thyroid carcinoma may account for local invasion but not on the depth of airway disease. The AMES score identifies men older than 40 years and women older than 50 years with major involvement of the thyroid capsule as a high-risk group [36]. The European Organization for Research and Treatment of Cancer (EORTC) system labels tumors with fixation or infiltration of adjacent structures as T3 and adds a weight factor for local invasion of any depth [37]. The MACIS [38] and AGES [39] scores also add a weight factor, while the TNM system does not account for local invasion [40].

Surgical Management

Resection of the airway for laryngotracheal invasion may be considered in five different clinical settings, each with different prognostic implications and treatment goals.

1. Incidental, asymptomatic adherence of the gland to the airway at initial thyroidectomy.
2. Early referral after incomplete tangential excision of thyroid cancer.
3. Transmural invasion with airway obstruction or hemoptysis prior to surgical therapy.
4. Local recurrence with airway obstruction late after thyroidectomy.
5. Malignant airway obstruction in the presence of distant metastatic disease.

Treatment with curative intent appears possible in categories 1 through 3, though recurrence in group 3 is common due to advanced disease. Palliation alone is realistic in categories 4 and 5. The controversy over the extent of resection is greatest in the treatment of thyroid cancer with seemingly superficial adherence to the airway. The role of standard en bloc resection, and of shave resection, in this group of patients remains unclear. The surgical alternatives will be discussed in ascending order of extent of resection.

Tangential Excisions of Tumor

Shaving. This technique consists of sharp separation of the gland from the wall of the airway with a knife. Often the surface of the trachea is scraped or tangentially cut to remove a further layer of airway tissue for microscopic analysis. Melliere and colleagues shaved off any tight adherence of the gland, occasionally cutting into tracheal rings; with evidence of deep tracheal invasion, electrocautery was applied on the tracheal wall or tracheal resection was selected [10]. The lack of a clear margin constitutes the main concern regarding this technique. Frazell and Foote [9], also quoted in Djalilian [8], stated "one can be reasonably certain that such sharp dissection does not remove all tumor cells". They warned of late reactivation of disease with penetration of the trachea, obstruction, and hemorrhage. The purpose of tangential excision is to achieve long-term control of thyroid carcinoma as long as no gross disease remains [29]. Nishida and coauthors saw no indication for tracheal resection in those carcinomas that abutted the external perichondrium and performed a shave resection [6]. Shin and coworkers [28], however, showed that there is no continuous plane underneath the "external perichondrium" since the peritracheal fascia is virtually continuous with dense fibrous tissue between the tracheal rings. Further, the perithyroidal adventitia and the lymphatics of the tracheal mucosa communicate in the intercartilaginous spaces, allowing tumor to spread into the trachea. Ozaki and colleagues performed circumferential tracheal resection and reconstruction in 21 patients and discovered that disease extended beyond the tracheal adventitia in 18 cases [41]. While luminal disease in 6 of 18 patients might have been diagnosed by bronchoscopy, Ozaki notes that carcinoma between

tracheal rings in 2 and submucosal disease in 10 patients would have remained undiagnosed, had the thyroid gland been shaved off the airway.
Complete resection, while possible in shave resection, is difficult to confirm. McCarty and coauthors found that all of 35 shave procedures left microscopic residual disease on the trachea [19]. Six of the 35 patients developed locoregional recurrence for a rate of 17% after a mean follow-up of 81 months [19]. Only 4 of 16 patients with tracheal invasion reported by Park and colleagues remained disease-free during 70.7 month of follow-up after a cartilage-shaving procedure [5]; trachea and paratracheal space were the site of failure in 10 of the 12 patients and 7 died of disease. These reports suggest therefore that shave resection is incomplete and a high rate of local failure must be expected. These observations translate into rates of local recurrence after shave procedures that are higher by a factor of 8 relative to segmental airway resection [22]. Residual disease may grow over time, may permeate the adjacent organs, may metastasize, or dedifferentiate in histology, even if overall survival rates 10 or 20 years after resection do not decline in younger patients [42].

Window Resection. The creation of local defects in the wall of the airway probably originated from deep tangential excisions and represents an implicit recognition of transmural invasion. Window defects impose limits on the extent of resection in length and circumference and leave a reconstructive problem. To avoid an unstable tracheal lumen, no more than a fraction of the circumference, and approximately 35% of the cricoid cartilage, may be resected [43]. Most resected patients require airway protection with a tracheostomy. The method of confirming the margin status is haphazard and positive margins are often left behind. Two patients so treated and referred to Massachusetts General Hospital for repair of the tracheal defect were found to have positive margins in all four quadrants of the windows [44]. Primary reconstructive options for a window defect are limited and consist of local muscle or myoperichondrial flaps [43]. Suture closure of a window defect is rarely possible. Given the safety of circumferential tracheal resection, there is no clinical role for window resection.

Tracheal or Laryngotracheal Sleeve resection
Tracheal sleeve resection was initially applied to invasive thyroid carcinoma after successful reconstruction for postintubation strictures and primary tumors [45-47]. The operation consists of en bloc resection of thyroid gland and attached trachea. Incidentally discovered invasion is often limited to two or three tracheal rings, allowing a short tracheal resection. Such an operation is not complex in experienced hands and adds little time to an unhurried thyroidectomy. Most reported surgical series originate from thoracic surgical centers with an interest in tracheal disease and contain predominantly patients with recurrent disease. The series of tracheal resection for thyroid cancer began with Ishihara and colleagues' report on 11 patients with papillary carcinoma, including a small number of patients treated with incomplete shave resection [48]. Separate thyroidectomy preceded tracheal resection in 73% of their patients [48], 46 of 82 patients (56%) in our series [32], and 11 of 18

patients (61%) in Tsumori and associates' study [18]. The advantages of this approach include a full thickness specimen of the trachea with precise determination of invasion depth and margin status, information on prognosis [28], immediate reconstruction of the airway, and rarely a need for tracheostomy. The operation is performed preferably as an en bloc resection, with attached thyroid gland, although a discontinuous resection, shortly after thyroidectomy, may also be done. This technique is suitable at the time of primary resection, with or without immediate histologic confirmation of invasion, or for treatment of a local recurrence. Tumor involving the lower larynx may be resected in continuity, reconstructing the subglottic airway with the trachea shaped to conform to the cricoid or thyroid cartilage defect [44,49]. Ishihara and associates performed anterior cricoid resection in 2 of 11 patients [48], while laryngotracheal reconstruction was needed more commonly in our hands (58%, 40 of 69 patients) [32].

Operative risk in centers experienced in tracheal surgery is low when patients with high-dose preoperative radiation or cervical exenteration for recurrent disease are excluded. Including such high-risk patients, Grillo and colleagues reported 3 operative deaths (8.8%) of whom 1 occurred from anastomotic separation after cervical radiation with 7800 cGy and 1 after cervicomediastinal exenteration [44]. Excluding these high-risk patients in our most recent series, the mortality in patients undergoing airway reconstruction measures 1.4% (1/69) [32]. The single death was due to anoxic brain injury from airway obstruction after laryngotracheal reconstruction. Temporary tracheostomy was required in 18.8% and a permanent airway tube in 4.3%. Ozaki and associates reported 21 tracheal sleeve resections without operative mortality, and only one patient required tracheostomy for bilateral vocal cord palsy [41]. Tsumori and associates reported 13 patients with tracheal resection and end-to-end anastomosis without operative death [18]. Ishihara and colleagues reported no operative death in 24 patients undergoing sleeve resection for invasion, a 28% rate of postoperative laryngeal stenosis in the entire group, and a 8% rate of anastomotic stricture [1]. Wada and co-workers experienced no critical operative complications in 13 cases of complete en bloc resection [50]. Musholt and associates initiated tracheal and laryngotracheal resection in an endocrine surgical unit after gaining experience with shave and window techniques. They observed 1 death after 6 laryngotracheal resections (17%) and none after 5 tracheal resections [51]. In 6 window resections, there was 1 death due to an innominate artery fistula; permanent or prolonged tracheostomy was necessary in 29% of shave resections and 3 of 6 window resections (50%). Thus segmental tracheal resection adds a very small risk of major complications or death to thyroidectomy, while voice, respiration, and deglutition are preserved.

Total Laryngectomy and Cervical Exenteration

Laryngectomy and cervical exenteration are salvage resections for patients with extensively invasive primary disease or locoregional recurrent disease following previous resection or radiation. Exenteration refers to the combined removal of

larynx, pharynx, cervical esophagus, thyroid, and lymph nodes with intestinal reconstruction using stomach (gastric pull-up), jejunum or colon [52]. The indications for total laryngectomy without reconstruction are laryngeal destruction or permanent glottic dysfunction due to bilateral vocal cord palsy. Exenteration encompasses resection of the esophagus with reconstruction of swallowing by either gastric, jejunal or colonic transposition. Depending on the length of resected trachea, a cervical or mediastinal tracheostomy is constructed [53]. The operation should remove all gross tumor to provide meaningful palliation. Postoperative hypoparathyroidism may occur. In the report of Grillo and colleagues [44], seven patients underwent cervical exenteration. Three of these had no prior surgical therapy, and 4 previously underwent thyroidectomy. One patient (17%) died of perforated peptic ulcer and a leak of the esophageal closure; other complications included respiratory failure and transient hemiplegia after division of the right carotid and innominate artery in 1 each, and stenosis of the tracheal stoma in 3. Of 6 operative survivors, 2 patients died of progressive disease, 3 died late of other causes, and 1 was alive less than 2 years after surgery.

Other Palliative Resection

Resection of the airway in carefully selected patients with advanced locoregional or distant disease provides meaningful palliation of airway bleeding or obstruction. The aim is to reduce the risk of tracheal hemorrhage and the need for an airway tube without performing a complete regional resection. Segal and co-workers observed hemoptysis or airway obstruction in 7 of 15 patients after thyroidectomy with or without tracheostomy and lymph node dissection, but in none of 13 patients following laryngectomy or partial tracheal resection in addition to thyroidectomy [17]. In the most recent update of the MGH experience, 5 patients with distant metastasis at operation did not have local recurrence after airway resection, and of 9 other patients with distant disease at operation who later developed local recurrence, only 2 required an airway tube [32].

Non-surgical management

Radioactive Iodine

The indication for radioactive iodine (RAI) therapy alone is metastatic or locally advanced disease when surgical options are exhausted. The role of orally RAI has not been separately investigated in airway invasion. Postoperative adjuvant therapy for residual disease in the tracheal wall may have limited effectiveness for two reasons. As noted above, tumors invading the airway are less differentiated, may take up less RAI and therefore be resistant to therapy. When tracheal tumor burden is large, a larger proportion of RAI is taken up, sparing microscopic disease elsewhere. Despite these caveats, adjuvant RAI as postoperative treatment is commonly administered after all types of resection.

External Beam Radiation Therapy (EBRT)

Adjuvant or palliative radiation is commonly proposed for locally advanced cancer after incomplete resection. The benefit of EBRT in thyroid cancer, however, is controversial. In patients with known residual disease in the neck, EBRT may improve local control [54,55]. The use of adjuvant radiation in patients with resected locally advanced disease improved recurrence rates in one study [56] while another showed no benefit [57]. EBRT is not a substitute for complete removal of the tumor. Further, prior radiation vastly increases the risks associated with future airway resection, even when vascularized tissue such as omentum protects the healing tracheal anastomosis.

Outcome Parameters

Reports of surgical treatment for airway invasion usually contain a mix of operations with curative and palliative intent. A summary of results is provided in Table 3 [6,18,19,22,26,32,50,51,58,59]. Overall survival for well-differentiated tumors conveys little information regarding the success of resection. Local control and disease-free survival rates are more accurate, specifically when buttressed with follow-up examinations including thyroglobulin level, ultrasound, iodine scans, and bronchoscopy. A good example was provided by McCarty and colleagues who compared the rates of overall survival, disease-free survival, and local control in 40 patients with laryngotracheal invasion (Table 4) [19]. While the overall 10-year survival of patients with well-differentiated carcinoma and shave resection was 90.8%, the disease-free survival was only 50.9%. A 28.1% rate of overt local failure 10 years after thyroidectomy is unsatisfactory when life expectancy exceeds three decades.

Table 4. Comparison of Outcome Measures by McCarty et al. [19] in Patients with Differentiated Thyroid Carcinoma Invading the Trachea Treated with Cartilage Shaving

Outcome Measure	5-year (%)	10-year (%)
Overall survival	90.3	85.3
Local control rate	95.2	71.9
Disease-free survival	76.6	49.9

Table 3. Management and Outcome in Patients with Thyroid Carcinoma Invading the Airway

							Survival data according to type of resection[†]									
							All cases		Shave		Radical		Window		Incomplete	
First author	Year	N+ (%)	M1 (%)	Recurrent disease (%)	WD (%)	Mean follow-up (years)	No.	5-year %	No. (%)	5-year %	No. (%)	5-year %	No. (%)		No. (%)	5-year %
Tsumori [18]	1985	-	-	38.9	78	2.9	28	46			64	60				
McCaffrey [58]	1994	-	-	0	100	13	126	79 (63) [54]	-	90 (70) [60]	-	95 (90) [70]			-	65 (45) [40]
McCarty [19]	1997	62.5	0	0	88	6.8	40	89 (84)	88	90 (85)	12	68% FOD[*]				
Nishida [6]	1997	82.6	18.8	23.2	100	5.5	69		19	80 (68)	61	62 (43)				
Musholt[‡] [51]	1999	78.8	18.2	51.5	88	3.5[††]	33	-	48	19 ms	33	8 & 37 ms	18	12 ms		
Nakao [59]	2001	19.4	9.7	-	100	7.5	31	77 (68)			100	77 (67)				
Tsai [22]	2005	61.8	5.9	8.8	100	5.8[**]	34	86	47	84	53	88				
Segal [26]	2006	-	-	-	88	10.3[††]	49	78	67	79	33	75				
Wada[‡‡] [50]	2006	-	37.5	-	100	7.7	64		52	92 (88) [81]	20	84 (63)			28	44 (11)
Gaissert [32]	2007	42.7	20.7	56.1	75.6	6.1	82	52 (35) [22]			100	52 (35) [22]				

[†] Numbers in parenthesis: 10-year survival rate. Numbers in brackets: 15-year survival rate

[*] After 5 years of follow-up, 4 of 6 patients were free of disease

[‡] Survival stated as median survival. Median survival 8 months in circumferential resection, 37 months in step resection

[††] Follow-up duration in alive patients

[**] Median follow-up period

[‡‡] Disease-specific survival stated. Conservative resection group consisted of 13 shave excisions and 20 partial resections such as window resection

N1 = presence of lymph node metastases, M1 = presence of distant metastases, WD = well-differentiated, ms = months

Outcome measures after resection performed with palliative intent focus on freedom from airway obstruction, hemoptysis, and airway tubes in the survival period. Of 7 patients in the series of Grillo and colleagues who underwent airway resection in the presence of pulmonary metastasis, 2 with undifferentiated carcinoma survived less than one year, but during a mean survival of 4.2 years the remaining patients were free of airway events [44]. Quality of life for patients with thyroid carcinoma invading the airway improves after tracheal resections with end-to-end anastomosis [21,51,60,61]. Resection of the trachea invaded by tumor appears largely to accomplish the goals of preventing the dire late problems of airway obstruction and hemorrhage.

Discussion

Once thyroid carcinoma has transgressed the glandular capsule, invasion into the airway wall leads to a reduction in local control and survival. Four of the 5 staging systems for thyroid cancer acknowledge the negative prognostic impact of local invasion. The accelerated progression of disease in the years after diagnosis of luminal tracheal invasion is not controversial. A separation of these tumors into those with superficial and deep invasion is artificial and inadequate to guide treatment selection. There is now clear evidence of a higher rate of local recurrence and death after tangential shave resection for presumed superficial invasion. Conversely, immediate airway resection is associated with longer disease-free survival compared to later resection at the time of recurrence [32]. No oncologic data exist to support an incomplete resection for curative intent. Partial thickness invasion of the tracheal wall should therefore be regarded as an earlier stage of transmural invasion and treated with sleeve resection of the airway.

The surgeon unfamiliar with the techniques of tracheal resection has three options when encountering tracheal invasion. Operative exploration without thyroidectomy, leaving complete, combined resection to the surgeon trained in thyroid and airway procedures. Alternatively, combined resection may be performed by a multidisciplinary team of thyroid and tracheal surgeons. If thyroidectomy has been completed with a shave resection, tracheal or laryngotracheal resection may then be performed after referral to a surgeon or center experienced in airway surgery. Observation alone of a potentially invaded trachea not proven to be tumor-free is less than ideal given the option of tracheal and laryngotracheal resection in centers with experience in airway surgery.

Long-term (> 10 to 20 years) follow-up studies with detailed clinical and pathologic data including serum thyroglobulin levels, ultrasound examination, thyroid scans, and bronchoscopy to measure local recurrence and survival are scant or non-existent. The burden of proof rests on surgeons continuing to use shave resection, and based on the literature and our experience, we advocate tracheal resection when indicated.

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CHAPTER FIVE

5.2 – Segmental Laryngotracheal and Tracheal Resection for Invasive Thyroid Carcinoma

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ABSTRACT

Background: Laryngotracheal invasion worsens prognosis in patients with thyroid carcinoma. The extent of resection is controversial.

Methods: We performed a retrospective study of patients with thyroid carcinoma and invasion of larynx or trachea between 1964 and 2005.

Results: Eighty-two patients, mean age 64 years and 50% female, underwent segmental airway resection. Differentiated carcinoma was present in 76% (62/82), prior tracheal "shave" procedures in 40% (33/82), transmural invasion in 58% (48/82), and preoperative vocal cord paralysis in 35% (29/82). There were 29 tracheal and 40 laryngotracheal resections (*Reconstruction* group, 69 patients); 5 had laryngectomy, 7 cervical exenteration and 1 tracheal resection after exenteration (*Salvage* group, 13 patients). Operative mortality was 1.2% (1/82) and anastomotic dehiscence 4.3% (3/69). Tracheostomy was permanent in 4.3% (3/69). Mean follow-up was 6.1 years. Following *Reconstruction*, mean survival was 9.4 years and 10-year survival 40%, after *Salvage*, 5.6 years and 15%. In differentiated carcinoma, thyroidectomy, immediate shave procedure and delayed (mean 67 months) resection of airway recurrence in 15 patients resulted in overall and disease-free survival of 13.1 and 5.1 years, compared to 17.9 and 14.6 years after thyroidectomy and early airway resection in 11 patients. Airway symptoms, metastases at presentation, recurrent disease and salvage operation were associated with decreased survival; airway resection early after thyroidectomy, complete resection, and well-differentiated tumors with improved prognosis.

Conclusions: Segmental airway resection for invasive thyroid cancer is safe, preserves voice, and relieves airway obstruction. Complete resection of laryngeal and tracheal invasion during or early after thyroidectomy is associated with improved survival.

Introduction

The prognosis of patients with well-differentiated thyroid carcinoma is excellent, with a 10-year survival rate close to 90% after surgical resection [1]. Laryngeal or tracheal invasion, found in approximately 6% of thyroid carcinoma [2], is an independent predictor of death [3]. Advanced invasion may produce hemoptysis, hoarseness and dyspnea and leads to life-threatening complications such as airway hemorrhage and suffocation. Indeed, airway obstruction is the cause of death in 50% of patients with thyroid carcinoma [4]. These observations emphasize the importance of local control in both early and advanced airway invasion.

In thyroid carcinoma, complete resection of local disease provides the longest survival and the best palliation. In pursuit of this goal, segmental laryngotracheal and tracheal resection have been applied at Massachusetts General Hospital (MGH) to patients with superficial and transmural invasion of the airway. While segmental resection is widely accepted for transmural invasion [3,5-7], adherence to the trachea or larynx due to superficial invasion, in contrast, often is treated with tangential excision from the airway ("shaving"), even though this technique violates oncologic principle and falls short of complete resection [2]. Long-term evidence supporting tangential excision is absent, and recurrence is common [8-10]. Our approach was previously reported [11,12] and is now updated to analyze long-term results in a larger group of patients.

Patients and Methods

Patient Selection

Between 1964 and July 2005, 113 patients were seen with thyroid carcinoma invading larynx or trachea. Thirty-one patients (27.4%) were excluded from further analysis. Disease was not resected in 28 patients due to extensive local disease, advanced distant disease, or refusal of surgery. Three patients in the early experience of Grillo and colleagues [11,12] were excluded because their treatment is now obsolete: 2 had skin tube reconstruction of the trachea using cervical skin supported with plastic rings, a technique not used since and considered unnecessary; 1 who presented after high-dose (78 Gy) external beam radiation elsewhere experienced anastomotic dehiscence following tracheal reconstruction. Two of the 3 patients were operative deaths. The remaining 82 patients (72.6%) constitute the study population.

The 82 patients were classified according to clinical presentation and extent of disease. Twenty-eight patients presented with locoregional recurrent disease late after prior thyroidectomy (Delayed Presentation), while 11 patients were either referred for tracheal resection directly after thyroidectomy (8 patients) or underwent airway resection (3 patients) at the time of thyroidectomy (Early Presentation). There were 26 patients without previous thyroidectomy who had either airway obstruction

or hemoptysis due to transmural disease (Symptomatic Presentation). Finally, 17 patients had symptomatic airway disease and distant metastasis (Palliative Presentation). In the Early Presentation group, no patient had hemoptysis or dysphagia and only 1 who at first refused resection had dyspnea.

Pathology reports, operative reports, and hospital charts were reviewed. The survival period began on the day of operation at MGH, except where otherwise indicated. The MGH institutional review board approved previous retrospective studies and the most recent protocol in August 2005. Consent was received from patients before obtaining follow-up information.

Determination of Resectability

Patients underwent assessment of locoregional and distant metastatic disease before resection. Radiographic evaluation included conventional tracheal tomography in the early experience and computed tomography thereafter. Limited presumed or known pulmonary metastasis was not a contraindication to resection. Bronchoscopy was performed before resection to assess presence and extent of luminal invasion. Tracheal resection was considered when complete resection of gross airway disease appeared feasible. Symptomatic airway involvement was an indication for palliative resection even when grossly positive peritracheal margins or pulmonary metastasis were noted. A tumor was considered unresectable when advanced metastatic disease was present, the length of involved airway at bronchoscopy precluded primary anastomosis or mediastinal tracheostomy, or when invasion of vital adjacent organs was found during operative exploration.

Types of Resection

For tracheal resection, a segment of trachea was removed with end-to-end reconstruction. For laryngotracheal resection, the tumor was removed with a portion of infraglottic larynx, shaping the remaining trachea to reconstruct the laryngeal defect. These procedures belonged to the *Reconstruction* group and required at least one functioning recurrent laryngeal nerve not involved with tumor. When preoperative unilateral vocal cord paralysis was present, the contralateral thyroid lobe was often preserved. Invasion of esophageal muscle or mucosa was treated with tangential resection of full-thickness wall or muscle coat. The procedures in the *Salvage* group, cervicomediastinal exenteration or laryngectomy alone, were considered in patients who had airway compromise due to malignant airway stricture or aspiration with or without impaired swallowing. Exenteration and intestinal substitution was performed when the larynx could not be salvaged and consisted of laryngectomy, resection of trachea, esophagectomy, total thyroidectomy and usually parathyroid resection with creation of a cervical or mediastinal tracheal stoma. Locoregional lymph nodes were resected except for paratracheal nodes not immediately adjacent to tumor, which were preserved to protect tracheal blood supply. Absence of tumor at the airway margins was confirmed by frozen section unless the limits of resection had been reached and no additional trachea could be

removed without sacrificing larynx. The resection was judged to be complete when airway margins were found to be free of disease, soft tissue margins were not grossly involved with tumor, and no statement in the operative note indicated that gross tumor remained.

Tumor Data

Tumor dimension in the airway axis, depth of invasion, and the presence of tumor at airway or radial margins were recorded from a review of pathology reports. Positive airway margins indicated true residual, most often microscopic, tumor. Tumor involvement of excised lymph nodes was noted. To analyze the extent of invasion, the Shin staging system was used for well- (papillary and follicular carcinoma) and poorly differentiated thyroid carcinoma [13].

External Beam Radiotherapy and I-131 Therapy

Postoperative radiotherapy or oral radioactive iodine therapy were administered selectively when the resection was incomplete. After bronchoscopic assessment of anastomotic healing, a recommended dose of 54 Gy to the neck and superior mediastinum was administered 6 to 8 weeks after resection, following bronchoscopic check of the anastomosis. Most patients received treatment outside MGH, and the decision to administer adjuvant therapy was made elsewhere.

Follow-Up

Patients and their physicians were contacted for follow-up information. The social security death index was searched. Patients were determined to have died if name, date of birth, and social security number matched.

Statistical Analysis

Overall and disease-free survival after airway resection were calculated using the Kaplan-Meier procedure with the log rank test implemented in the SPSS 12.0 statistical software program (SPSS Inc., Chicago, IL). In patients presenting with airway recurrence only, the date of tracheal resection concluded the disease-free survival after previous thyroidectomy. To compare overall and disease-free survival after thyroidectomy with shave excision of the airway to thyroidectomy with immediate or early tracheal resection, the survival period was calculated from the date of first thyroidectomy.

Results

Patient Characteristics

The characteristics of 82 patients are listed in Table 1 according to the type of resection and airway reconstruction. Overall, well-differentiated tumors were found in 62 patients (75.6%), in 72.5% of patients undergoing *Reconstruction* and in only 38.5% of the *Salvage* group. Pathologic evaluation identified transluminal tumors (Shin stage IV) in 48 patients (58.5%).

Table 1. Characteristics of 82 resected patients with thyroid carcinoma invading the airway. Reconstruction consisted of primary airway anastomosis; resection for salvage included

	Reconstruction		Salvage		Overall		p-value
	n	%	n	%	n	%	(X^2)
N	69	84.1	13	15.9	82	100.0	
Mean age (median) *in years*	63.9 (66)		64.0 (67)		63.9 (66)		
Sex							0.131
Male	32	46.4	9	69.2	41	50	
Female	37	53.6	4	30.8	41	50	
Prior thyroidectomy	39	56.5	7	53.8	46	56.1	0.858
Prior shaving	29	42.0	4	30.8	33	40.2	0.745
Previous I-131	29	42.0	5	38.5	34	41.5	0.811
Previous XRT	6	8.7	4	30.8	10	12.2	0.026
Transluminal disease	42	60.9	6	46.2	48	58.5	0.323
Laryngotracheal resection	40	58.0			40	58.0	
Complete resection	36	52.2	8	61.5	44	53.7	0.535
Adjuvant RAI	28	40.6	3	23.1	31	37.8	0.233
Adjuvant XRT	24	34.8	4	30.8	28	34.1	0.780
Common symptoms							
Hemoptysis	19	27.5	1	7.7	20	24.4	0.126
Dyspnea, wheezing	18	26.1	7	53.8	25	30.5	0.046
Mass	26	37.7	2	15.4	28	34.1	0.120
Vocal cord paralysis	25	36.2	4	30.8	29	35.4	0.706
Asymptomatic	8	11.6	0	0.0	8	9.8	0.196
Histologic type							
Papillary	50	72.5	5	38.5	55	67.1	0.017
Follicular	6	8.7	1	7.7	7	8.5	0.905
Anaplastic	3	4.3	4	30.8	7	8.5	0.002
Huerthle cell	3	4.3	0	0.0	3	3.7	0.444
Oxyphillic	2	2.9	1	7.7	3	3.7	0.398
Squamous cell	1	1.4	1	7.7	2	2.4	0.181
Medullary	1	1.4	0	0.0	1	1.2	0.662
Undifferentiated giant cell	1	1.4	0	0.0	1	1.2	0.662
Carcinosarcoma	0	0.0	1	7.7	1	1.2	0.020
Poorly differentiated	2	2.9	0	0.0	2	2.4	0.534

Operative treatment

In the *Reconstruction* group, 40 patients underwent laryngotracheal resection (58%) and 29 tracheal resection (42%). One patient had a tracheal resection for primary tracheal neoplasm with skin tube reconstruction 31 years before presenting with a new papillary thyroid carcinoma invading her skin tube. She underwent resection of thyroid and skin tube with primary tracheal end-to-end anastomosis. A single patient had a wedge resection of the anterior tracheal wall early in the experience. Three patients (4.3%) underwent concomitant lateral excision of full-thickness esophageal wall with primary closure and 10 patients (14.5%) had excision of esophageal muscle for tumor invasion. The length of the resected airway measured 1.5 to 6.0 cm

(mean 3.2 cm). Resection was complete in 36 patients (52.2%). In 33 patients with incomplete resection, 4 had residual gross disease. Microscopic positive resection margins in 29 patients consisted of 25 positive airway margins, 3 uncertain airway margins with positive soft tissue margins, and 1 positive soft tissue margin only. Residual gross disease was due to distant metastases in 3 and the single wedge resection in 1. Five patients with incomplete resection had prior total thyroidectomy; all others underwent thyroidectomy.

In the *Salvage* group, 7 of 13 patients underwent cervical exenteration, 4 patients laryngectomy without esophagectomy, 1 laryngectomy with partial lateral esophagectomy, and 1 underwent tracheal resection after exenteration and tracheostomy. In patients with exenteration, the larynx was spared in 1 patient and the esophagus was reconstructed with colon interposition in 3, gastric pull-up in 2, a pectoralis flap in 1 and primary reconstruction in 1. Esophageal muscle was partly excised in 3 of 4 patients undergoing laryngectomy without esophagectomy. Mean length of resected airway was 9.1 cm (range 3.0 to 15.5 cm, the latter length including larynx). Complete resection was accomplished in 8 patients (61.5%).

Complications

The single death resulted from airway obstruction due to glottic edema after laryngotracheal resection. Table 2 lists the complications after *Reconstruction* and *Salvage*. Anastomotic dehiscence occurred in 3 *Reconstruction* patients (4.3%). Two had laryngotracheal reconstruction and were treated with temporary tracheostomy for less than a month. The third patient, in whom 4.5 cm of trachea were resected with laryngeal release, died 7 months later from respiratory failure. After *Salvage*, 2 patients with separation of tracheal stoma from skin were treated with a stomal stent. Hypoparathyroidism occurred in only 2 patients after *Salvage* (15.4%) and 3 after *Reconstruction* (4.3%). Four of 6 patients with postoperative aspiration developed pneumonia. Postoperative dysphagia was observed in 3 patients, of whom 2 had lateral esophageal resection.

Table 2. Complications after Reconstruction and Salvage (n). Percentages in parenthesis

	Reconstruction	Salvage	Overall
N	69	13	82
Hypoparathyroidism	3 (4.3)	2 (15.4)	5 (6.1)
Aspiration	5 (7.2)	1 (7.7)	6 (7.7)
Dysphagia	3 (4.3)	0	3 (3.7)
Anastomotic dehiscence	3 (4.3)	2 (15.4)	5 (6.1)
Bilateral vocal cord paralysis	6 (8.7)		6 (8.7)
Temporary tracheostomy	13 (18.8)		13 (18.8)
Permanent tracheostomy	3 (4.3)		3 (4.3)
Other	7 (10.1)	7 (53.8)	14 (4.9)
Mortality	1 (1.4)	0	1 (1.2)
No complications	44 (63.8)	6 (46.2)	50 (61.0)

Five of 6 patients in the *Reconstruction* group with postoperative bilateral vocal cord paralysis had preoperative unilateral paralysis, and the contralateral recurrent laryngeal nerve was preserved in 4. Four of 6 had temporary tracheostomy from 1 to 9 months: 3 required vocal cord lateralization and 1 had spontaneous vocal cord recovery less than 1 month after operation. The indications for temporary tracheostomy in 13 of 69 patients (18.8%; mean duration 2, range 0 to 9, months) were bilateral vocal cord paralysis in 4, anastomotic dehiscence in 2, aspiration pneumonia in 1 and dyspnea from subglottic edema in 1. Five were placed for protective reasons during operation. Three patients required permanent tracheostomy (4.3%): 1 patient with anastomotic dehiscence and respiratory failure described above, 1 who died 10 months after operation from metastatic disease, and 1 patient who died 2 months after resection from myocardial ischemia. The incidence of complications decreased over 4 decades to 25.8% from 1996 to 2005. Postoperative adjuvant therapy is detailed in Table 1.

Long-term Results

The mean follow-up period was 6.1 years (range 2 months to 24 years). Follow-up was complete in all patients. Of 65 patients surviving the operation without permanent tracheostomy, 11 patients had only local recurrence treated with an airway tube in 4, 7 patients had distant recurrence only, 6 patients had both distant and local recurrence treated with an airway tube in 2, 5 patients with distant metastasis at operation did not develop local recurrence, and of 9 other patients with distant disease at operation who later developed local recurrence, 2 required an airway tube. In total, 8 patients received an airway tube due to local recurrence. Table 3 shows overall and disease-free survival in the *Reconstruction* and *Salvage* groups. Figure 1 depicts the survival curves of *Reconstruction* and *Salvage* groups.

Table 3. Overall and disease-free survival (DFS) in Reconstruction and Salvage groups

	Overall (n=82)	Reconstruction (n=69)	Salvage (n=13)
Mean survival (years)	8.93	9.45	5.56
5-year survival (%)	52	55	38
10-year survival (%)	35	40	15
15-year survival (%)	22	23	15
Mean DFS (years)	5.35	6.07	2.67
5-year DFS (%)	33	34	23
10-year DFS (%)	16	21	0
15-year DFS (%)	14	18	0

Figure 1.

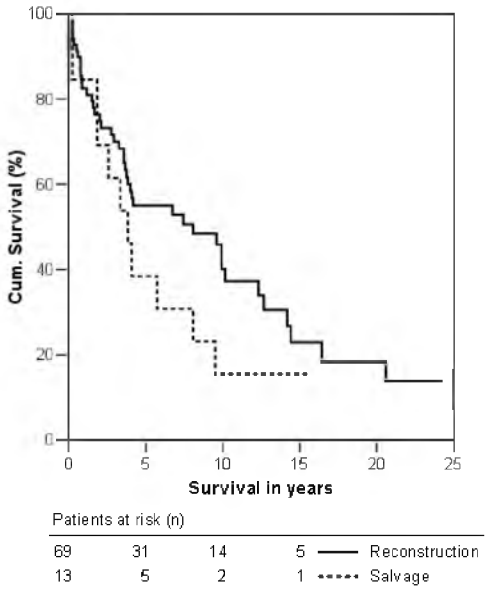


Figure 2.

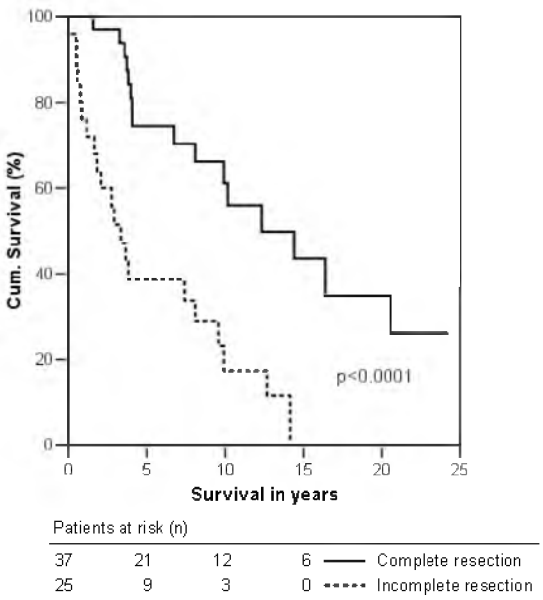
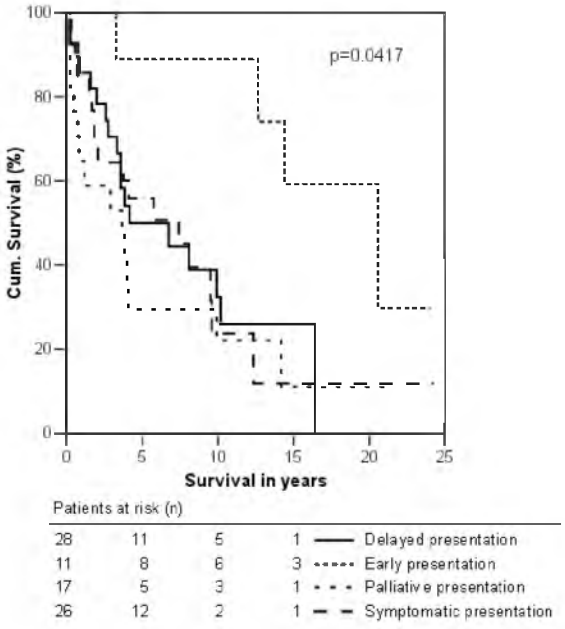


Figure 3.



Figures 1-3. Survival curves by 1. Reconstruction and Salvage groups; 2. Complete and incomplete resection in well-differentiated carcinomas (n=62); 3. Type of presentation

Sixty-two patients with well-differentiated thyroid carcinoma were analyzed separately. Overall and disease-free survival is shown in Table 4. After complete resection, mean survival was 13.8 years and survival at 15 years 44%. As shown in Figure 2, after incomplete resection mean survival was only 5.3 years and none of

the patients is alive at 15 years (p<0.0001). Disease-free survival was also significantly higher in patients with complete resection (p=0.0053).

As shown in Figure 3, there is a marked difference in survival between asymptomatic patients undergoing airway resection at the time of thyroidectomy or early thereafter in comparison with all other groups. The prognosis after Delayed, Symptomatic, or Palliative Presentation is worse compared to patients with Early Presentation (p=0.0417). Palliative resection, however, in some patients is compatible with long-term survival. Three patients are presently alive 5, 11 and 21 years after palliative airway resection.

Table 4. Overall and disease-free survival (DFS) in well-differentiated thyroid carcinoma

				Complete resection	
	Overall (n=62)	Reconstruction (n=56)	Salvage (n=6)	Yes (n=37)	No (n=25)
Mean survival (years)	10.23	10.57	6.11	13.77	5.34
5-year survival (%)	60	63	33	74	39
10-year survival (%)	42	45	17	61	17
15-year survival (%)	25	26	17	44	0
Mean DFS (years)	6.45	7.02	1.67	8.53	2.94
5-year DFS (%)	37	41	0	50	18
10-year DFS (%)	22	25	0	28	14
15-year DFS (%)	19	22	0	28	7

Survival after Thyroidectomy

We identified 15 patients with well-differentiated histology and recurrent disease after shave procedure (Delayed Airway Resection group) among 28 with prior thyroidectomy and compared them to 11 patients who underwent early airway resection (Early Airway Resection group). Characteristics of these groups are described in Table 5. Three of the 15 patients belonged to a low-risk age group [14] at the time of thyroidectomy (2 women less than 50 years, 1 man less than 40 years of age) and 11 (73.3%) had received radioactive iodine therapy after thyroidectomy. One patient, counted as an early resection, was referred immediately following thyroidectomy and tracheostomy, but did not present for laryngotracheal resection until 14 months later.

Figure 4 compares the overall survival of patients with early shave procedure and late airway resection for recurrence after a mean delay of 67 months to those who underwent immediate or early airway resection. Mean survival calculated from the date of thyroidectomy in the Delayed group was 13.1 years and 20-year survival 24%, lower than following early airway resection. Disease-free survival after early airway resection was significantly higher (p=0.0092) than after delayed resection (14.6 vs. 5.1 years; Figure 5), and disease-free survival at 20 years was also significantly higher (50 vs. 0%).

Table 5. Characteristics of patients with delayed vs early airway resection after thyroidectomy

	Delayed Airway Resection		Early Airway Resection	
	n	%	n	%
N	15		11	
Mean age at thyroidectomy* *in years*	59.7 (34-79)		60.3 (17-79)	
Sex				
Male	5	66.7	5	45.5
Female	10	33.3	6	54.5
Well-differentiated histology	15	100.0	11	100.0
Papillary carcinoma	12	80.0	10	90.9
Positive lymph nodes at thyroidectomy	4	26.7	4	36.4
Distant metastasis at thyroidectomy	0	0.0	0	0.0
Mean interval thyroidectomy - airway resection* *in months*	62 (13-202)		3 (0-14)	
Shin stage at airway resection				
I	1	6.7	4	36.4
II	1	6.7	1	9.1
III	2	13.3	3	27.3
IV	11	73.3	3	27.3

* Numbers in parentheses: range

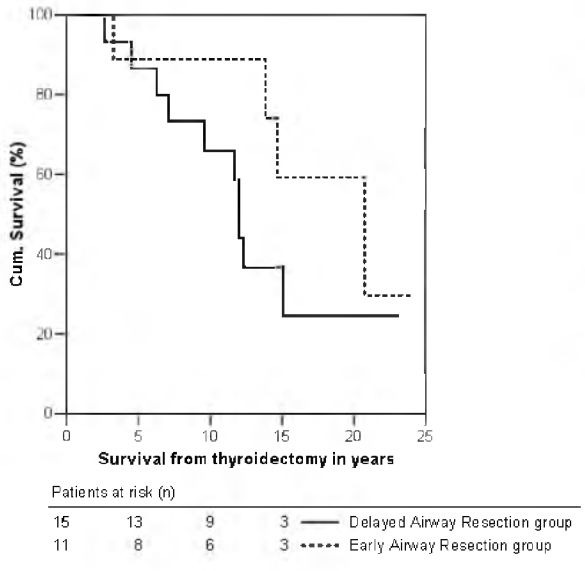


Figure 4. Survival calculated from the date of thyroidectomy

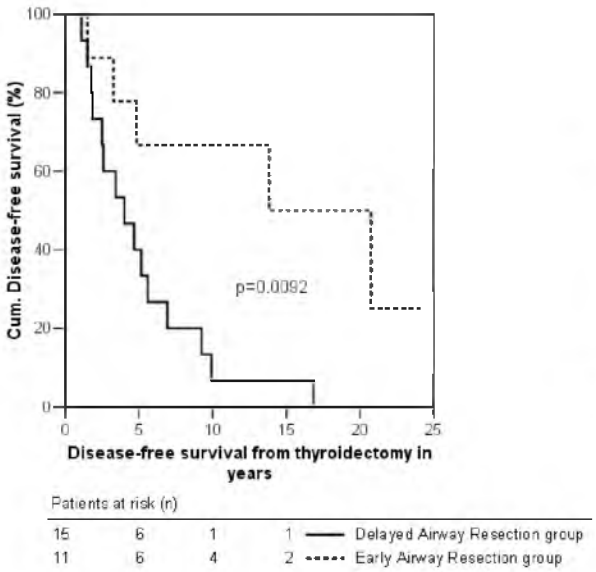


Figure 5. Disease-free survival calculated from the date of thyroidectomy

Discussion

The present study confirms in a large group of patients the safety and effectiveness of segmental tracheal resection noted in the earlier reports from our unit. With increasing experience and when considering presently applied indications and procedures, the operative mortality has declined to 1.2% and the complication rate decreased from 44% to 26% over the last three decades. These results are substantiated by Ozaki [15], Tsumori [1], Ishihara [4], and their colleagues who saw no operative deaths in a combined 58 segmental tracheal resections. Operative risk should therefore not serve as the reason to forgo complete resection of thyroid cancer involving the airway, though operative risk remains a function of surgical experience [16,17].

Shave or tangential excision appears to be common and preferred surgical management for airway invasion. More than half of all patients in our study treated with segmental laryngotracheal and tracheal resection (46/82) had prior resection of thyroid carcinoma, and 33 of these underwent so-called "shave" procedures. The proponents of shave procedures point to lack of data on the prognosis of airway invasion, to available adjuvant external beam radiotherapy (EBRT) and radioactive iodine (RAI), and to concerns about quality of life after tracheal resection. Czaja and associates compared 34 patients who underwent complete surgical resection of tumor with 75 patients who had shave excision and found no differences in survival between both groups [3]. Nishida and colleagues agreed that survival in 40 patients with deep tracheal invasion treated with tracheal resection was no different than that in 13 patients with superficial invasion treated with a shave [6]. Because a tracheal specimen does not accompany the thyroid after tangential excision, we do not know the presence or depth of invasion in the two studies above. There is now sufficient evidence to state that depth of invasion predicts outcome [1,13]. In long-term studies, other authors emphasize the high risk of recurrence following excision of airway invasion by thyroid carcinoma. Six of 35 patients with superficial tracheal adherence treated with tracheal shaving in a study by McCarty et al. had local recurrence after 10 years (17%) [5]. Seven of 16 patients after shave procedures treated with RAI or EBRT after operation died of disease 3.6 years after surgery, and disease was controlled in only 25% of patients after 5.9 years [8]. In contrast, local airway recurrence after segmental tracheal resection is infrequent. Following 31 patients for a mean of 10.6 years after resection, Nakao and colleagues [19] found only 2 local among 12 total recurrences (6.5%). The high recurrence rates reported above by Park and associates [8] occurred despite RAI or EBRT. In our group of 15 delayed airway resections for well-differentiated carcinoma, 11 patients had received RAI therapy after thyroidectomy (73.3%). We observed airway recurrence requiring tracheostomy in 12.3% (8/65). Since the surgical technique to achieve complete resection is well established, a reliance on RAI or EBRT following shave procedures is difficult to justify and may be futile. Finally, the quality of life after segmental airway

resection in patients with thyroid carcinoma involving the airway is higher than before operation [17,18].

Immediate or early complete resection of laryngotracheal invasion is followed by the longest overall and disease-free survival. We found complete resection a significant prognostic factor, and positive airway margins defined a majority of patients with incomplete resection (79%, 26/33). We also identified in this retrospective analysis a comparable set of patients mainly distinguished by the date of airway resection after thyroidectomy. When determining survival from the date of the first thyroidectomy as the start of follow-up, and after adding a mean survival period of more than 5 years to patients who presented after shave resection for delayed airway resection, we found a persistent benefit of early airway resection for differentiated thyroid carcinoma. The two groups had minor differences in the proportion of female patients, though not in age at first resection or absence of distant metastasis. Overall survival calculated from the date of first thyroidectomy was longer after early airway resection, though not significant due to sample size. Disease-free survival, however, was significantly higher after early resection, with 10- and 20-year disease-free survival rates of 67% and 50%, while after delayed resection disease-free survival at 10 years was only 7% and none of the patients was alive without disease after 20 years. The purpose of such comparison, exposed as it may be to selection bias, is of course not to replace, but to provoke, an overdue prospective multi-institutional study of the surgical options in laryngotracheal invasion.

Palliative resection offers benefit in terms of survival or quality of life in few solid tumors. The patients presenting with distant metastasis had a mean survival of 6 years after segmental airway resection. Even in the presence of distant metastasis, segmental airway resection may prolong survival, control disease and lead to long term survival in some patients [19]. We therefore continue to apply palliative tracheal resection in carefully selected patients.

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CHAPTER SIX

General Discussion

This thesis describes two unusual types of cancer both localized in the trachea, namely primary tracheal carcinoma (Chapters 2, 3 and 4) and thyroid carcinoma invading the trachea (Chapter 5), focusing on the treatment of these cancers, and addressing existing controversies and shortcomings in the management of patients with these rare tumors.

Primary Tracheal Carcinoma

In Chapter 3.1, it is shown that in resected squamous cell carcinoma (SCC) of the trachea, irradical resection, involvement of the thyroid gland, and lymphatic invasion are histopathologic features with important negative prognostic value. Contrastingly, as described in Chapter 3.2, in adenoid cystic carcinoma (ACC) of the trachea, invasion of adjacent organs does not seem to affect survival. En bloc resection of invaded organs, such as the thyroid or the esophageal muscle coat, resulted in acceptable long-term survival, as long as negative radial margins could be obtained. Lymph node invasion and perineural invasion were also important negative predictors of survival. No statement on the absence or presence of perineural invasion was included in the pathology report in 55% of cases. Given its important impact on survival, we recommend to always include a statement regarding perineural growth in the pathology reports describing all specimens of tracheal tumors.
For both studies on tracheal SCC and ACC, it is important to realize that the conclusions are based on resected cases only. Tumors growing into vital organs such as the heart or the great vessels and tumors involving long segments of airway judged unresectable were not included in these studies.

In both tumors, one of the most important prognostic factors was completeness of resection. Gaissert previously described that survival in patients with unresectable tracheal cancer is dismal [1]. In addition, long-term survival (> 10 years) is observed after tracheal resection of locally advanced ACC (Chapter 3.2). Thus tumor resectability, usually dictated by tumor length in the long axis of the airway and invasion of vital organs, is possibly the single most important prognostic factor in this very distinct type of cancer. In future research, the possible roles of HPV-infection, K-ras mutation, EGFR and possibly more mutations should be further investigated focusing on relation of prognosis and individual treatment planning.

Undertreatment of Primary Tracheal Carcinoma

Comparing population-based studies and surgical series in Chapter 2, there are several striking differences. First, the incidence of ACC proved to be lower in studies derived from epidemiologic data: 3-21% [2-7] compared to 30-60% in clinical series [1,8-14]. Second, the rate of patients undergoing surgical resection in population-based studies is around 10% [2-6], while in series from clinics with experience in tracheal resections, around 70% of patients are treated with surgery [1,15]. Third, a relatively

high incidence of small cell carcinoma (6-7%) is found in population-based studies [2,5], while this histologic type is virtually never reported in clinical series [9].
The study undertaken in the Netherlands described in Chapter 4.1 of this thesis confirms all the above mentioned findings that were previously reported in population-based studies from the United Kingdom [5,6], Finland [16], Japan [3], Denmark [2] and the United States [7]. In the Netherlands, ACC accounted for only 7% of all tracheal malignancies, 12% of patients underwent resection and small cell carcinoma was found in 11% (Chapter 4.1). Of 22 patients with ACC, 11 (50%) were treated with surgery, making up 32% of the group of surgically treated patients (Chapter 4.1). However, in series from Canada and China, around 80% of patients with ACC were resected [15,17].

As surgery is the best curative treatment modality currently available, it is important to determine what the reasons are for the discrepancy in treatment pattern between population-based studies and several large clinics. Part of this striking difference is likely based on the referral function that centers with experience in the management with tracheal tumors have, leading to a highly selected population in reports from these clinics. However, taking this factor into account, Gaissert and Hazama stated that at least half of all patients with tracheal carcinoma in the general population should be candidates for surgical resection [9,11]. Gaissert also stated that due to the absence of radiologic and pathologic review of cases in population-based studies, some cases might be misclassified as primary tracheal tumors [9]. The relatively high incidence of small cell carcinoma (6-11%) is an important sign of this contamination with metastatic, mainly bronchial, carcinoma [18].
To determine the proportion of patients registered in the Netherlands Cancer Registry (NCR) with tracheal cancer whose radiographic findings are consistent with the diagnosis and who are candidates for surgical resection, a nationwide audit of cases was conducted as described in Chapter 4.2. Of 101 registered cases in the period 2000-2005, 34 (34%) were other primary tumors misclassified as tracheal cancer. This finding in combination with earlier results described in Chapter 4.1 (0.142 per 100,000) leads to an estimated incidence of approximately 1 case of primary tracheal carcinoma per one million persons per year. Based on the results from the audit, one can assess that ACC makes up around one quarter of all tracheal carcinomas, while SCC accounts for around half of all cases. In the process of registration in the NCR, results of any biopsy of malignant cells from the trachea are reported to the NCR automatically as tracheal cancer by the national pathology database (PALGA). The final registration in the NCR database, however, involves a review of the complete medical file. Thus, reasons for this misclassification may be administrative in the NCR registration, incomplete disclosure of surgery reports, typing errors or misclassification by doctors.
Since population-based studies based on Finnish [4] and Danish [2] cancer registries found 27% and 12% misclassified tumors even without radiologic review of all cases, this is likely an internationally existing problem that should be addressed, at least

partially by adapting the registration process. This could lead to a more correct registration of rare airway tumors in the future.

Fifty patients with primary tracheal carcinoma and sufficient data were available for the multidisciplinary panel of specialists and second reviewer to judge respectability. Of those, 12 patients had been treated with surgery, while both panel and second reviewer identified 16 additional surgical candidates, a total of 28 (56%). Of 13 patients with ACC, 10 (77%) were judged to be candidates for surgical resection, while only 7 of these (54%) had actually undergone surgery. These findings indicate that there might be an undertreatment of this rare airway tumor in the Netherlands, and, in view of the similar results in other population-based studies, likely in more countries. The concept of unsolicited panel and radiographic review of all registered cases of a certain type of tumor in one country in a designated period by external auditing of blinded and abstracted data by a panel of experts is unique in its design. It approximates the concept of multidisciplinary oncologic review by local experts adopted for common tumors in everyday practice. However, the method itself is subject to limitations, the most important being that not all specialists have had personal contact with the patient. Treatment advice of our panel review was however highly reproducible: the inter-reviewer disagreement between panel and second reviewer was small (8%).

Potentially Too Conservative Treatment of Thyroid Carcinoma Invading the Airway

Controversy exists on the extent of resection needed to treat thyroid carcinoma appropriately if the tumor has invaded the airway. One of the most important issues that leads to this controversy is selection bias in clinical studies. In most studies comparing conservative “shave” excisions with segmental airway resection, shave excision is only applied to superficially invasive carcinomas, while segmental airway resection is reserved for, often recurrent, tumors extensively invading the larynx and or trachea [19,20]. As discussed in Chapter 5.1, there is however clear evidence of a higher rate of local recurrence and death after shave resection even in patients with superficial invasion [21-23]. Conversely, segmental airway resection is associated with longer disease-free survival compared to delayed resection when recurrent disease has been diagnosed (Chapter 5.2).
As reported in Chapter 5.2, the mortality and complication rates have dropped to 1.2% and 26% in the last three decades. Although operative risk remains a function of surgical experience [24,25], it should not serve as a reason to forgo complete resection of thyroid cancer involving the airway. Moreover, the quality of life after segmental airway resection in patients with thyroid carcinoma involving the airway is higher than before the operation [25,26]. No data exist to support an incomplete resection for curative intent in oncology practice. Partial thickness invasion of the tracheal wall should probably be regarded as an earlier stage of transmural invasion and treated with sleeve resection of the airway. This implies that in the situation

where airway invasion is diagnosed pre-operatively, consultation of an experienced airway surgeon is recommended for adequate planning of the operation including en bloc resection of thyroid and the diseased part of the airway. When, more commonly, involvement of the larynx or trachea is found unexpectedly during thyroidectomy, we advocate consulting with an airway surgeon intra-operative or directly post-operative to warrant immediate or early resection of the remaining part of the tumor in the airway wall by means of a segmental airway resection and reconstruction.
Although thyroid carcinoma invades the airway in 6% of cases, this scenario lacks in the Dutch guideline on thyroid carcinoma (Centraal Begeleidings Orgaan, CBO, 2007) [27]. However, the guideline emphasizes that any patient with thyroid carcinoma should be treated in a multidisciplinary team and that all patients with lymph node metastasis and / or recurrent disease should be treated in a multidisciplinary team in a highly specialized centre (level 1 hospital) [27]. In this respect, airway-involvement should be regarded as the same serious stage of disease.

Centralization

In rare diseases such as tracheal tumors, the pool of experts is small and often not local. We believe that each patient diagnosed with a tracheal tumor should be referred to a tertiary oncology center with multidisciplinary experience in the treatment of tracheal tumors. Given the rarity of the disease, to warrant sufficient exposure to (malignant) tracheal pathology and to maintain experience, one center per each population of an estimated 10 to 20 million would be optimal. In such a centre, approximately 10 to 20 patients with primary tracheal cancer would be managed by a multidisciplinary team of specialists and an estimate of 5 to 10 patients would eventually be operated on. In the Dutch situation with a population of 16.5 million inhabitants (Centraal Bureau voor de Statistiek, CBS, 2009), this would mean one national center. By centralizing the care for patients with this rare airway tumor, more patients may be selected for surgical resection, thus potentially improving survival outcome and quality of care. Because this improvement is inferred but untested, close evaluation would be needed once a centralized system is implemented to assess the exact benefit of this new strategy. Similar centralization has been organized in the Netherlands for much more frequent malignant tumors like esophageal cancer and gynecological cancers. This process was driven by studies relating volume and outcome in these cancers [28-30], but also in other patients groups like lung cancer and head and neck cancer the evidence for centralization is increasing.
In the Netherlands, these insights ultimately led to a report from the Dutch Cancer Society in which is concluded that oncologic care in the Netherlands should be centralized in (high-volume) centres by 2012. As a rule, an oncologic surgeon should only perform a procedure when a volume criterion of at least 10 per year is met.

Future developments

On a final note, one issue that should not be left unaddressed is the ongoing quest for a material with which large post-resection tracheal defects can be reconstructed, as primary reconstruction with end-to-end anastomosis can usually only be achieved under acceptable tension in defects less than 50% of tracheal length. Replacement of the trachea is difficult, because the material should be rigid laterally and flexible longitudinally and should have an epithelialized lumen. Attempts at creating a material that meets these requirements have been undertaken for decades. Despite efforts, there has not been much success in animal and clinical studies [31]. However, some encouraging results have been achieved. The group of Carpentier transplanted aortic allografts in 20 sheep and found that the tubes were epithelialized with mucociliairy epithelium and contained newly formed cartilage rings [32]. Wurtz and colleagues successfully used this technique in two patients as reported in the New England Journal of Medicine in 2006 [33]. Biopsy after one year showed respiratory epithelium, and the patients are breathing well after 18 months of follow-up with the silicone stent still in place. In 2008, the group of Macchiarini and Birchall published a case in The Lancet in which the left mainstem bronchus was replaced with a de-cellularized and de-antigenized donor tracheal transplant colonized by the recipients epithelial cells and chondrogenic mesenchymal cells [34]. Although the follow-up in this case was only two months, these results are promising for the future of tracheal replacement, which is still the 'holy grail' of airway surgery. Very recently, Delaere from the Leuven University (Belgium), presented the first successful case of a vascularized tracheal allotransplantation at the European Respiratory Society meeting (Vienna, Austria, September 2009; no reference yet available).

Conclusion

In summary, complete segmental resection for primary tracheal carcinoma and thyroid carcinoma invading the airway, when feasible, is currently the best treatment modality available leading to good long-term outcome. The fact that, in general, only 10-25% of patients are treated with surgery is likely based on undertreatment of this disease. Although currently still widely applied, conservative shave resection for invasive thyroid carcinoma leads to a marked increased risk of local recurrence compared to segmental airway resection.
To improve patient care and survival outcome, the management of these rare tumors in the airway should always involve a tertiary center with experience in the multidisciplinary treatment of tracheal tumors. For this reason the Dutch Centre for Central Airway Diseases as part of the Radboud University Nijmegen Medical Centre will be launched in 2010.

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CHAPTER SEVEN

Summary

In this thesis, several aspects of malignant tumors located in the trachea are expounded and issues concerning the treatment of patients with these rare types of cancer are discussed.

Chapter 2 describes the clinical aspects and treatment of primary tracheal malignancies by reviewing the available literature on this topic. New diagnostic, staging and treatment guidelines are proposed. One of the key elements in the workup of patients with tracheal cancer is selecting patients that are candidates for surgical treatment, as surgical resection and primary reconstruction is the best curative treatment modality available at present.

Chapter 3 focuses on the pathologic characteristics of the two most common types of tracheal cancer, squamous cell carcinoma and adenoid cystic carcinoma (ACC). These histopathologic features are correlated with clinical outcome, to investigate which of these characteristics can be used to help predicting survival in patients with these tumors.

In **Chapter 3.1**, the pathologic characteristics of 59 cases of resected squamous cell carcinoma (SCC) of the trachea are described. SCC is the most common primary tumor of the trachea. A classification for the manner and depth of invasion appropriate for tracheal resections is proposed. Three factors were very important predictors of outcome: incomplete resection, extension of the tumor into the thyroid gland and lymphatic invasion or lymph node metastases all lead to very unfavorable prognosis. It is thus very important for the surgeon to establish clean lines of resection, using as appropriate intraoperative frozen section. Keratinization, dyskeratosis, acantholysis, necrosis, and tumor thickness, had no discernible prognostic value.

Chapter 3.2 describes the prognostic value of pathologic characteristics and resection margins in 108 cases of tracheal adenoid cystic carcinoma (ACC). ACC is the second most common primary tracheal tumor, known for its tendency to exhibit extensive submucosal and perineural spread. A resection with tumor-free margins may therefore be difficult to achieve. This could also be appreciated in our study; airway margins were grossly positive in 8%, microscopically positive in 55% and negative in 37%. Adventitial margins of transmural sections were grossly positive in 3%, microscopically positive in 88% and negative in only 9%. Overall survival and disease survival were highest in patients with negative resection margins, followed by microscopic positive resection margins, followed by a very poor (disease-free) survival in patients with gross positive margins. Absence of extramural disease was a positive prognostic factor, while invasion of adjacent organs did not significantly impact (disease-free) survival. Perineural growth was present in 34%, absent in 11% and not noted in the pathology report in 55%. Because the presence of perineural growth was a negative prognostic factor, it is emphasized that this feature should always be looked for by the pathologist and noted in the pathology report. A positive

lymph node biopsy led to a decline in (disease-free) survival. These results show that even in patients with advanced disease, tracheal resection can lead to long-term survival (> 10 years).

Chapter 4 sheds light on the treatment of tracheal cancer in the Netherlands. Both studies incorporated in this chapter have been conducted in collaboration with the Netherlands Cancer Registry.

In **Chapter 4.1**, the incidence, characteristics, treatment and survival of patients with tracheal cancer in the Netherlands is mapped for a 14-year period from 1989 to 2002. In total, 308 cases could be identified, an annual incidence of 0.142 per 100,000 inhabitants. Of the 293 patients diagnosed while alive, only 12% underwent surgical resection, while 53% received radiotherapy, and 35% neither. Median survival was only 10 months, with 5-year and 10-year survival rates of 15% and 6%, respectively. Survival in patients who underwent surgical resection was much higher: 51% after 5 years and 33% after 10 years. These results support the good outcome reported in the literature describing series of patients with tracheal cancer treated with surgery. Some authors have suggested that at least 50% of patients with tracheal cancer should be candidates for surgical resection. In other European countries, it was also found that that only 12% of tracheal cancer patients were treated with surgery. The question is raised what proportion of patients with primary tracheal carcinoma really are surgical candidates and why only little over 10% are currently treated with surgery.
To address these questions, the study described in **Chapter 4.2** was undertaken. A medical audit based on national epidemiologic data was conducted. Blinded patient data and radiologic images were reviewed by a multidisciplinary panel and a second reviewer to assess diagnosis and resectability. One third of NCR-registered primary tracheal carcinomas were misclassified non-tracheal primaries involving the trachea. In 50 cases confirmed by panel and second reviewer, actual treatment consisted of surgery in 24%, radiotherapy in 58%, endobronchial treatment in 12%, and observation in 6%. Both panel and second reviewer identified 16 additional surgical candidates, a total of 56%. A majority of cases meeting audit criteria for diagnosis and surgical resection was treated with other modalities. This study suggested that incorrect diagnosis and undertreatment are common in rare airway tumors.

Chapter 5 deals with thyroid carcinoma growing into the larynx or trachea. A review of the literature on the management of thyroid carcinoma invading the larynx or trachea is given in **Chapter 5.1**. Controversy exists on the extent of resection needed in case of invasion of the larynx or trachea by thyroid carcinoma, usually found intra-operatively during thyroidectomy. The technique of shaving off the thyroid carcinoma from the airway evades resection of the airway but poses a marked risk of local recurrence. Circumferential sleeve resection of larynx and trachea are safe and lower the risk of local recurrence. In recurrent disease, laryngotracheal resection can provide effective palliation of airway obstruction and hemoptysis. In view of the slow

growth of thyroid carcinoma, long-term (>10 to 20 years) prospective studies are required to compare the outcome after shave excision with segmental airway resection.

Chapter 5.2 describes the results of segmental laryngotracheal and tracheal resection for invasive thyroid carcinoma in 82 patients. There were 69 reconstructive operations and 13 salvage operations. Overall operative mortality was 1.2%. After reconstructive operations, anastomotic dehiscence occurred in 4.3% and tracheostomy was permanent in 4.3%. Airway symptoms, metastases at presentation, recurrent disease and salvage operation were associated with decreased survival. Airway resection early after thyroidectomy, complete resection, and well-differentiated tumors led to more favorable prognosis. Segmental airway resection for invasive thyroid cancer is safe, preserves voice, and relieves airway obstruction. When thyroid carcinoma is found to invade the larynx or trachea during thyroidectomy, complete resection including segmental airway resection and reconstruction should be performed during or early after thyroidectomy, as this management is associated with improved survival compared with shaving and delayed airway resection.

In conclusion, the treatment of patients with a rare tumor of the airway should always be situated in an experienced center with multidisciplinary experience in the management of these tumors. This will improve the quality of care and probably the outcome of disease as well, by attacking the current undertreatment. Also, further research would be facilitated that could unravel many remaining questions that could not be answered yet.

APPENDICES

Dutch Summary (Samenvatting)
Acknowledgements (Dankwoord)
List of Publications
Curriculum Vitae

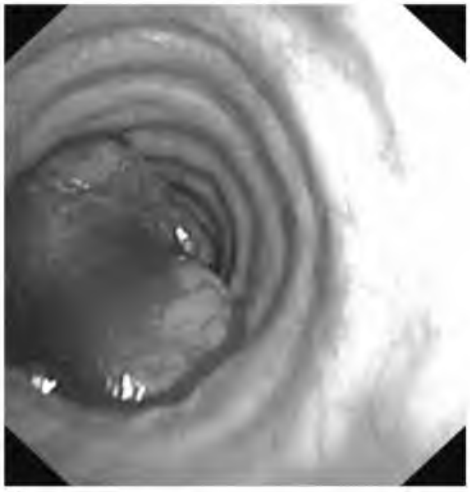
Appendix I

"Maligne Tumoren van de Trachea"

Dutch Discussion and Summary

Primair tracheacarcinoom

Maligne aandoeningen van de bovenste luchtwegen en de longen komen relatief frequent voor, in Nederland is de incidentie meer dan 10.000 per jaar [1]. Tracheatumoren vormen binnen deze groep een zeldzaamheid met een geschatte incidentie van ongeveer 1 op de miljoen inwoners per jaar [2]. Dit leidt er toe dat er doorgaans weinig bekendheid bestaat over de vergaande mogelijkheden van behandeling. Een chirurgische behandeling met en bloc verwijdering van de tumor in de vorm van een segmentale trachearesectie met een directe end-to-end anastomose reconstructie al of niet gevolgd door radiotherapie is doorgaans de meest aangewezen therapie in geval van een tracheacarcinoom [3].



Figuur 1. Endoscopisch zicht op een ernstige trachea obstructie ten gevolge van een adenoidcystischcarcinoom ten tijde van het stellen van de diagnose

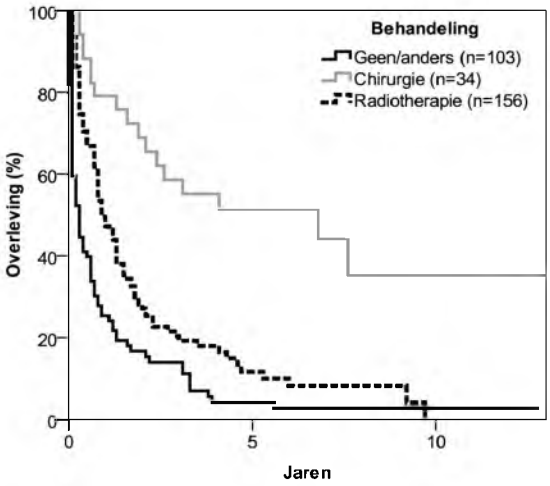
De meeste tumoren in de trachea zijn maligne [4] en bedreigen het leven van de patiënt niet alleen door luchtwegobstructie, maar ook door locoregionale invasie en eventuele metastasering op afstand. Omdat klachten van dyspneu en stridor pas ontstaan wanneer ongeveer 75% van het oppervlak van het tracheale lumen geobstrueerd is wordt de tumor vaak pas in een laat stadium gediagnosticeerd (Figuur 1). Op dat moment is de mate van luchtwegobstructie doorgaans levensbedreigend [5].

Meestal zijn er bij de patiënt al geruime tijd (maanden tot jaren) een hoorbare ademhaling en niet verontrustende klachten zoals lichte dyspneu bij inspanning en hoesten aanwezig [6]. Dit klachtenpatroon wordt nogal eens onterecht toegeschreven aan en behandeld als obstructieve longziekten zoals astma en COPD [7].

Onderbehandeling van primaire tracheatumoren

De meeste grote onderzoeken naar het voorkomen en het klinisch beloop van het tracheacarcinoom zijn vanwege de lage incidentie gebaseerd op landelijke of regionale gegevens van kankerregistraties van enkele decades. Er zijn wereldwijd slechts enkele centra met een dusdanig grote verwijzingsfunctie dat het zinvol is de resultaten van één kliniek te rapporteren als patiëntenserie [6,8-12]. Daarnaast zijn er nog enkele multi-centrum studies van klinieken met ervaring in de behandeling van tracheatumoren, zoals uit Frankrijk [13] of Japan [14].
Registratiegebaseerde studies uit het Verenigd Koninkrijk [4,15], Finland [16], Japan [17], Denemarken [7] en de Verenigde Staten [18] laten geheel andere resultaten zien dan de genoemde klinieken met ervaring in de behandeling van luchtwegtumoren. Het belangrijkste verschil is dat uit kankerregistratie-gebaseerde rapportages is gebleken dat slechts ongeveer 10% van alle patiënten met een tracheacarcinoom chirurgisch behandeld wordt, terwijl dit percentage in gespecialiseerde klinieken tussen de 60-80% ligt. Een deel van dit opmerkelijke verschil kan worden verklaard door een verschil van de onderzochte patiëntenpopulaties. Er valt bijvoorbeeld te verwachten dat patiënten met afstandsmetastasen niet, of zelden, verwezen worden naar een gespecialiseerde kliniek. Volgens Gaissert [19] en Hazama et al. [14] zou echter, na verdiscontering van deze factor, ongeveer de helft van de algehele populatie patiënten met een maligne tracheatumor een geschikte kandidaat voor chirurgische therapie zijn. Aangezien chirurgische behandeling de meest aangewezen curatieve behandeling vormt, is het belangrijk vast te stellen waarom slechts 10% van de patiënten in op populatie gebaseerde studies op deze wijze behandeld is. Licht et al. (Denemarken) stelden dat dit lage percentage mogelijk toe te schrijven is aan een nihilistische attitude gebaseerd op onvoldoende kennis van de chirurgische mogelijkheden bij tracheatumoren [7].

Nationale audit naar tracheatumoren in Nederland



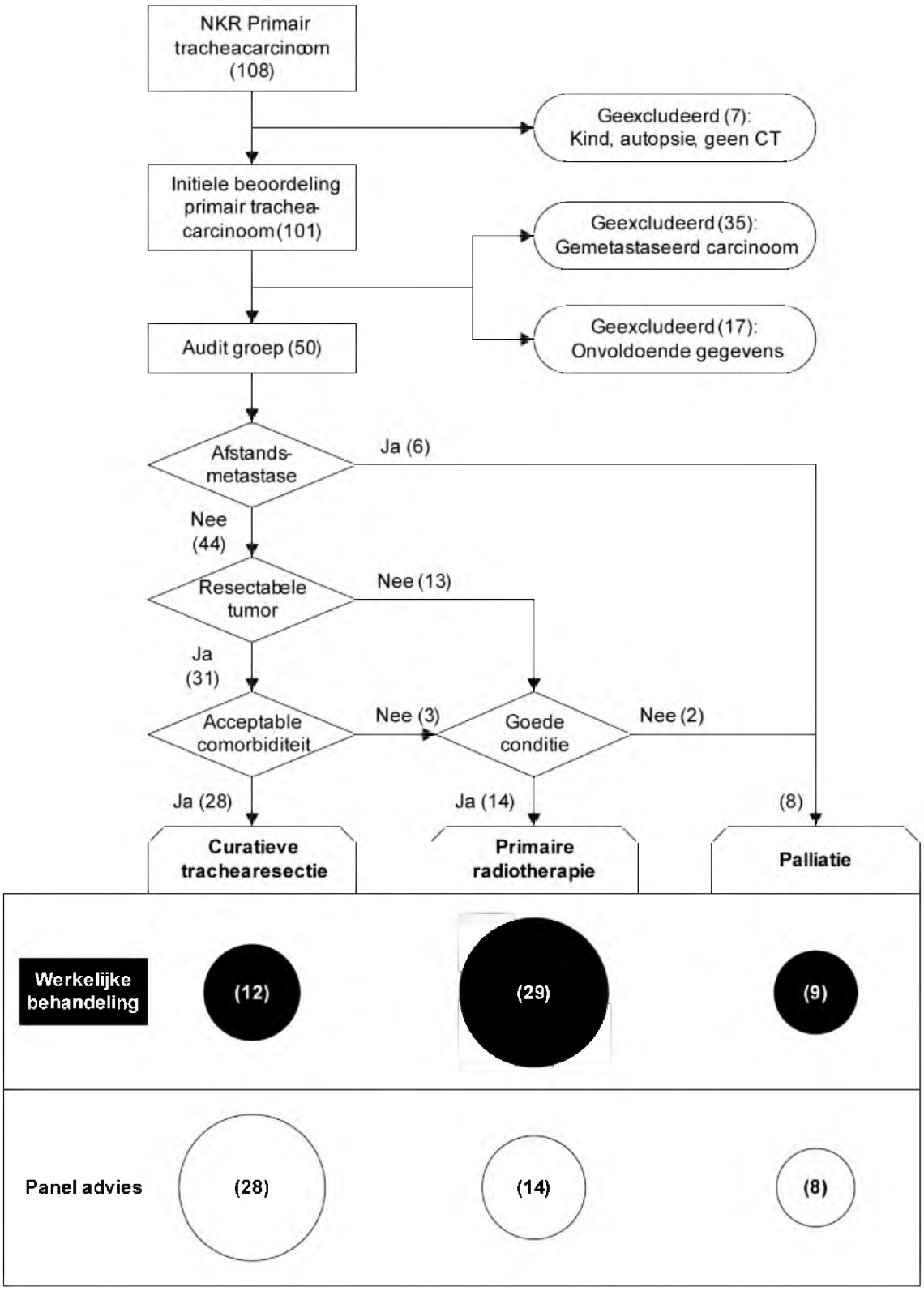
Figuur 2. Overleving van Nederlandse patiënten met een tracheacarcinoom naar behandeling [20]

Om de situatie in Nederland in kaart te brengen is in samenwerking met de Nederlandse Kankerregistratie (NKR) een landelijke studie uitgevoerd naar het voorkomen, de behandeling en de overleving van patiënten met een tracheacarcinoom [20]. Uit dit onderzoek is gebleken dat in Nederland in de 14-jaar tellende periode van 1989 – 2003 van de 293 patiënten slechts 12% werd behandeld met chirurgie, terwijl 53% primaire radiotherapie onderging. 35% heeft geen van beide, in potentie curatieve, behandelingen ondergaan.

In de gehele onderzoekspopulatie was de 5-jaars overleving 15%, terwijl deze voor chirurgisch behandelde patiënten 51% bedroeg (Figuur 2). Deze resultaten komen overeen met de eerder genoemde resultaten van de op kankerregistratie gebaseerde studies.

Naar aanleiding van deze resultaten rijst de vraag welk aandeel van alle patiënten met een primair tracheacarcinoom daadwerkelijk kandidaat is voor chirurgische behandeling. Om hier een antwoord op te kunnen geven werd een nationale audit gehouden [2]. Via de NKR werden van de jaren 2000 – 2005 alle patiënten met tracheacarcinoom geïdentificeerd. Via het Integraal Kankercentrum Oost (IKO), een van de 8 integrale kankercentra in Nederland, werden alle hoofdbehandelaars benaderd om hen toestemming te vragen voor inclusie van de desbetreffende patiënt(en). Alle behandelaars gaven hun toestemming om de patiëntengegevens uit de status, de thoraxfoto's en, indien van toepassing, CT- en MRI-scans van de afdelingen radiologie op te vragen. Al deze informatie werd verzameld, geanonimiseerd en gebundeld tot een samenvatting per patiënt. Een multidisciplinair team werd samengesteld bestaande uit een longarts, cardiothoracaal chirurg, radioloog, hoofd-hals oncologisch chirurg en twee radiotherapeuten. Op eenzelfde wijze als bij een tumorwerkgroep gebruikelijk is werd elke patiënt separaat besproken en naar aanleiding van de bovenbeschreven gegevens bepaald of het daadwerkelijk om een primair tracheacarcinoom ging. Daarnaast werd een advies uitgebracht over de te volgen behandeling. Vervolgens zijn alle casus opnieuw ter beoordeling voorgelegd aan een tweede beoordelaar, een thoraxchirurg van het Massachusetts General Hospital in Boston met een uitgebreide ervaring in de behandeling van patiënten met een tracheatumor. De gecombineerde mening van het multidisciplinaire panel en de tweede beoordelaar werd vergeleken met de werkelijke behandeling die de patiënt had ondergaan.

Zeven patiënten van de 108 NKR-geregistreerde patiënten werden uitgesloten: 2 maal werd de diagnose vastgesteld bij autopsie, 2 maal betrof het kinderen en 3 maal bleek de gemaakte CT-scan onvindbaar te zijn. Van de overgebleven 101 patiënten werd in retrospect de diagnose primair tracheacarcinoom verworpen in 34 gevallen (34%); in 20 gevallen was er sprake van een andere primaire tumor (long, slokdarm en larynx) en in 14 gevallen was er sprake van uitgebreide peribronchiale lymfadenopathie van een onbekende primaire tumor met doorgroei in de trachea. Daarnaast werden 17 patiënten geëxcludeerd omdat er onvoldoende klinische informatie beschikbaar was om een oordeel te vellen over de te volgen behandeling. Uiteindelijk bleven 50 patiënten over waarvoor het multidisciplinair panel en de tweede beoordelaar een behandeladvies hebben uitgebracht. Voor deze 50 patiënten was de werkelijke behandeling chirurgie bij 12 patiënten (24%), radiotherapie bij 29 (58%), endobronchiale behandeling bij 6 (12%) en expectatief beleid bij 3 (6%). Een patiënt werd alléén als chirurgische kandidaat beschouwd wanneer zowel panel als tweede beoordelaar als advies chirurgie gaven. Dit leverde 16 additionele chirurgische kandidaten op, een totaal van 28 (56%). Het panel en de tweede beoordelaar waren het in 4 gevallen oneens (8%).



Figuur 3. De tumor van een patiënt werd alleen als resectabel beschouwd indien resectie zowel door het panel als de tweede beoordelaar werd geadviseerd. De werkelijke behandeling (donkere ballonnen) wordt vergeleken met het oordeel van de audit (witte ballonnen) in 50 patiënten met primair tracheacarcinoom (p = 0.005). De oppervlakte van de ballonnen komt overeen met het aantal patiënten per groep. NKR = Nederlandse Kankerregistratie

Foutieve registratie en onderbehandeling van tracheatumoren in Nederland

Uit deze nationale audit blijkt dat ruim 1/3 van alle geregistreerde gevallen van tracheacarcinoom bij de NKR foutief geregistreerd zijn. De initiële (voorlopige) registratie in de NKR vindt plaats via een automatische koppeling met PALGA op basis van het aantonen van maligne cellen in de trachea. Deze cellen zouden evenwel afkomstig kunnen zijn van primaire long- of slokdarmtumoren met directe doorgroei in de trachea of lymfkliermetastasen in omliggende peribronchiale lymfklieren met invasie van de trachea. Definitieve registratie vindt echter pas plaats vanuit het volledige medisch dossier. Wellicht houden registratiemedewerkers te strikt vast aan de door PALGA opgegeven lokalisatie, maar een deel van de misclassificatie kan ook zijn ontstaan door een foutieve diagnose in het medisch dossier.
In eerdere studies uit Finland [21] en Denemarken [7] werden eveneens foutief geclassificeerde tumoren gevonden in respectievelijk 27% en 12% van het nationale cohort, terwijl in deze studies geen volledige beoordeling van de radiologische en klinische gegevens heeft plaatsgevonden. Misclassificatie van dit type tumor komt dus internationaal voor en dit geldt wellicht eveneens voor andere zeldzame vormen van kanker. Het is noodzakelijk dat het registratieproces van de NKR aangepast wordt om het aantal misclassificaties terug te dringen.
Meer dan de helft van de patiënten werd in de audit achteraf beoordeeld als chirurgisch kandidaat, terwijl slechts 24% deze behandeling had ondergaan. Dit suggereert een relatieve onderbehandeling van deze zeldzame tumor in Nederland. Gezien de overeenkomende getallen uit studies uit andere landen geldt dit waarschijnlijk zelfs internationaal. Hoewel het concept van een ongevraagde tweede mening op basis van beoordeling van klinische en radiologische gegevens van alle landelijk geregistreerde gevallen van een bepaald type tumor in een bepaalde periode uniek is, vertoont deze methode grote gelijkenis met de verschillende tumorwerkgroepen die in Nederland bestaan, waarbij patiëntencasus besproken worden door een vast team van specialisten van verschillende disciplines. Het grootste verschil is dat dit doorgaans geschiedt na verwijzing van de behandelend arts. Daarnaast was het verschil in de mening van het panel en de tweede beoordelaar klein (8%) en dus de reproduceerbaarheid groot.

Schildkliercarcinoom met invasie van de larynx of trachea

Schildkliercarcinoom is een relatief veel voorkomende tumor, die in Nederland jaarlijks bij ongeveer 3 per 100.000 inwoners voorkomt [1]. In de Verenigde Staten is de incidentie 14 per 100.000 inwoners [22] en was schildkliercarcinoom de zesde op de lijst van meest voorkomende maligniteiten in 2008 [22]. Ondanks het feit dat sterfte als gevolg van schildklierkanker ongebruikelijk is, wordt meer dan de helft van alle sterfgevallen als gevolg van schildkliercarcinoom veroorzaakt door luchtwegobstructie en –bloeding [23]. Invasie van de larynx of trachea komt voor bij ongeveer 5,8% van alle gevallen van schildkliercarcinoom [24]. Dit wordt echter zelden

gediagnosticeerd voorafgaand aan de gebruikelijke, waardoor de chirurgische planning niet gericht is op luchtwegchirurgie. In meer dan 80% van de gevallen van invasie van de luchtweg is dit onverwacht intra-operatief vastgesteld door de chirurg die de thyroïdectomie uitvoert [25].

Mogelijk te conservatief beleid bij schildkliercarcinoom met invasie van de luchtweg

Er bestaat een controverse met betrekking tot welke behandelstrategie adequaat is voor invasie van de luchtweg door schildkliercarcinoom. De belangrijkste oorzaak voor deze controverse ligt in het feit dat er geen gerandomiseerde studies zijn naar de twee belangrijkste chirurgische opties: conservatieve (oppervlakkige, "shave") verwijdering van de tumor versus en bloc segmentale resectie van het geïnvadeerde deel van de larynx of trachea. In de meeste studies waarin deze behandelingen vergeleken worden, wordt gekozen voor een conservatieve "shave" excisie indien de invasie van de luchtweg oppervlakkig is. Hierbij wordt tumorweefsel van de trachea afgeschraapt tijdens de thyroïdectomie. Een segmentale resectie van het betrokken deel van de trachea wordt met name toegepast bij tumoren die dieper of zelfs tot in het lumen van de luchtweg groeien, waarbij het vaak om recidieven gaat [26,27]. Hierdoor ontstaat waarschijnlijk een selectie bias ten voordele van de "shave" excisie.
De conservatieve "shave" excisie wordt toegepast ondanks duidelijke aanwijzingen dat hierbij de kans op lokaal recidief en sterfte als gevolg hiervan groter is dan na segmentale resectie [25,28,29]. Zo beschrijven McCarty et al. dat in alle 35 patiënten behandeld middels een "shave" excisie een microscopisch tumorresidu achterbleef op de larynx of trachea [25]. Analoog hieraan leidt onmiddellijke resectie van het aangedane segment van de luchtweg tot een langere ziektevrije overleving dan latere resectie van een recidief. De mortaliteit en morbiditeit van een trachearesectie in combinatie met een thyroïdectomie voor een schildkliercarcinoom met invasie in de luchtweg zijn in de loop der jaren gezakt naar 1,2% en 26%, respectievelijk [30]. Bovendien blijkt de kwaliteit van leven na segmentale trachearesectie in verband met een schildkliercarcinoom beter te zijn na de operatie dan voor de operatie [31,32]. Het operatieve risico zou dus geen reden mogen zijn een volledige resectie van de tumor achterwege te laten en te kiezen voor een conservatieve "shave" excisie, waarbij wel aangetekend moet worden dat de uitkomsten van de operatie afhankelijk zijn van de ervaring die de chirurg heeft met luchtwegchirurgie [31,33].
Er bestaat geen oncologische data die het toepassen van een incomplete resectie rechtvaardigt als curatieve therapie. Gedeeltelijke of oppervlakkige invasie van de luchtweg zou daarom beschouwd moeten worden als een eerder stadium van transtracheale invasie en zou dus behandeld moeten worden middels segmentale trachearesectie. Dit houdt in dat indien pre-operatief invasie van de luchtweg is gediagnosticeerd, de thyroïdectomie gecombineerd zou moeten worden met een trachearesectie door een chirurg met ervaring in de luchtwegchirurgie. Meestal wordt invasie van de larynx of trachea echter onverwacht opgemerkt tijdens de

thyroïdectomie. Wanneer dit het geval is, adviseren wij intra-operatief dan wel direct post-operatief een luchtwegchirurg te consulteren, zodat mogelijk direct tijdens de thyroïdectomie dan wel binnen enkele weken na de thyroïdectomie het residu van de tumor in de wand van de luchtweg verwijderd kan worden door middel van een segmentale luchtwegresectie.

Ondanks het feit dat schildkliercarcinoom in bijna 6% van de gevallen ingroei in de luchtweg vertoont, worden de consequenties voor de behandeling niet besproken in de Landelijke Richtlijn Schildkliercarcinoom van het Centraal BegeleidingsOrgaan (CBO, 2007) [34]. Deze richtlijn benadrukt dat iedere patiënt met een schildkliercarcinoom in een multidisciplinair team behandeld zou moeten worden en dat alle patiënten met lymfekliermetastasen en / of recidief ziekte bij voorkeur behandeld zou moeten worden in een level 1 ziekenhuis [34].

Centralisering van de zorg rondom patiënten met een zeldzame aandoening van de trachea

Bij zeldzame aandoeningen zoals tumoren van de trachea zijn er slechts weinig experts. Iedere patiënt waarbij de diagnose tracheatumor gesteld wordt, zou verwezen moeten worden naar een tertiair oncologiecentrum met multidisciplinaire ervaring in de behandeling van deze tumoren. Gezien de zeer lage incidentie, zou ongeveer 1 centrum per 10 a 20 miljoen inwoners een maximum zijn om te garanderen dat er voldoende expositie is aan (maligne) trachea pathologie. Hierdoor zou in een dergelijk centrum per jaar ongeveer 10 tot 20 patiënten gezien worden met een tracheacarcinoom. Van deze patiënten zou naar schatting 5 tot 10 patiënten een trachearesectie ondergaan. In de Nederlandse situatie met 16,5 miljoen inwoners (Centraal Bureau voor de Statistiek, 2009) betreft dit dus één nationaal centrum. Door deze hoge mate van centralisatie van zorg voor patiënten met deze zeldzame luchtwegtumor kunnen mogelijk meer patiënten geselecteerd worden voor chirurgische behandeling, hetgeen potentieel de overleving ten goede zou kunnen komen. Soortgelijke hoge mate van centralisatie is in Nederland al georganiseerd voor meer frequent voorkomende tumoren zoals slokdarmkanker en gynaecologische carcinomen. De drijvende kracht achter deze ontwikkelingen waren de studies waarin de relatie tussen volume van operaties per afdeling en resultaat werd aangetoond [35-37]. Ook in andere groepen zoals patiënten met longkanker en hoofd-hals kanker ontstaat steeds meer bewijs voor deze relatie. In Nederland heeft dit inzicht geleid tot een rapport van het Koningin Wilhelmina Fonds (KWF) dat is opgesteld door experts van de verschillende medische beroepsgroepen in de oncologische zorg en leden van de Integrale Kankercentra met ruggespraak met patiëntenorganisaties, de overheid, verzekeraars en ziekenhuizen [38]. Dit rapport wordt in 2010 gepubliceerd en zal er toe leiden dat de oncologische zorg in Nederland meer zal worden geconcentreerd [38]. Dit zal met name vruchten afwerpen voor de “hoog-complexe, laag-volume zorg”.

Conclusie

Samenvattend is een segmentale resectie van de luchtweg voor primair tracheacarcinoom en schildkliercarcinoom met invasie van de luchtweg veilig en leidt deze behandeling tot goede resultaten op langere termijn. Indien een chirurgische verwijdering technisch mogelijk is en de comorbiditeit van de patiënt het toelaat is dit momenteel de meest aangewezen behandelingsmogelijkheid, waarschijnlijk in minimaal de helft van de gevallen. Het feit dat over het algemeen slechts 10-25% van de patiënten met een primair tracheacarcinoom behandeld wordt met chirurgie komt minstens gedeeltelijk door onderbehandeling van deze aandoening.
Hoewel conservatieve “shave” excisie nog steeds veel wordt toegepast voor schildkliercarcinoom met invasie van de luchtweg, leidt dit tot een duidelijk verhoogd risico op lokaal recidief in vergelijking met segmentale resectie van de luchtweg.

Om de zorg voor en overleving van patiënten met een zeldzame tumor van de luchtweg te verbeteren zou de behandeling plaats moeten vinden in een tertiair kenniscentrum met ervaring in de multidisciplinaire behandeling van deze tumoren. Om deze reden zal het Radboud Centrum voor Centrale Luchtweg Ziekten als onderdeel van het Radboud Universitair Medisch Centrum te Nijmegen worden opgericht in 2010.

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Appendix III

List of Publications

Papers

- J. Honings, A.C. Weinberg, D.J. Mathisen, E.J. Mark, C.D. Wright, J.C. Wain, H.A. Gaissert. Prognostic Value of Pathological Characteristics and Resection Margins in Tracheal Adenoid Cystic Carcinoma. *Eur J Cardiothorac Surg. 2010 Mar 29 (Epub ahead of print).*

- J. Honings, A. Stephen, H.A.M. Marres, H.A. Gaissert. The Management of Thyroid Carcinoma Invading the Larynx or Trachea. *Laryngoscope. 2010 Apr;120(4):682-9.*

- H.A. Gaissert, J. Honings, M. Gokhale. Treatment of Tracheal Tumors. *Semin Thorac Cardiovasc Surg. 2009 Fall;21(3):290-5.*

- J. Honings, E.J. Mark, R. Ruangchira-Urai, J.C. Wain, C.D. Wright, D.J. Mathisen, H.A. Gaissert. Pathologic characteristics of resected squamous cell carcinoma of the trachea: prognostic factors based on an analysis of 59 cases. *Virchows Arch. 2009 Nov;455(5):423-9. Epub 2009 Oct 17.*

- M.J.F. de Wolf, J. Honings, F.B.M. Joosten, L. Hoefsloot, E.A.M. Mylanus, C.W.R.J. Cremers. Two siblings with progressive, fluctuating hearing loss after head trauma, treated with cochlear implantation. *J Laryngol Otol. 2010 Jan;124(1):86-9. Epub 2009 Jun 23.*

- J. Honings, H.A. Gaissert, A.F.T.M. Verhagen, J.A.A.M. van Dijck, H.F.M. van der Heijden, L. van Die, J. Bussink, J.H.A.M. Kaanders, H.A.M. Marres. Undertreatment of Tracheal Carcinoma: Multidisciplinary Audit of Epidemiologic Data. *Ann Surg Oncol. 2009 Feb;16(2):246-53. Epub 2008 Nov 27.*

- J. Honings, R.J.E. Pennings, L.H. Hoefsloot, F.B.M. Joosten, C.W.R.J. Cremers. Head Trauma as Eliciting Event for Transient Increased Sensorineural Hearing Loss and Vertigo in Pendred/EVA syndrome. *Int J Pediatr Otorhinolaryngol Extra. 2008 Dec;3(4):177-181.*

- H.A. Gaissert, J. Honings, H.C. Grillo, D.M. Donahue, J.C. Wain, C.D. Wright, D.J. Mathisen. Segmental Laryngotracheal and Tracheal Resection for Invasive Thyroid Carcinoma. *Ann Thorac Surg. 2007 Jun;83(6):1952-9.*

- H.F.M. van der Heijden, J. Honings, A.F.T.M. Verhagen, H.A.M. Marres. [Tracheal Tumors in the Netherlands]. Dutch title: "Tracheatumoren in Nederland". *Pulmoscript. 2007;17 (1): 44-48.*

- J. Honings, J.A.A.M. van Dijck, A.F.T.M. Verhagen, H.F.M. van der Heijden, H.A.M. Marres. Incidence and Treatment of Tracheal Cancer. *Ann Surg Oncol. 2007 Feb;14(2):968-76. Epub 2006 Dec 2.*

- J. Honings, A.F.T.M. Verhagen, H.F.M. van der Heijden, H.A.M. Marres. [Surgical treatment of tracheal carcinomas]. Dutch title: "De chirurgische behandeling van tracheacarcinomen". *Ned Tijdschr KNO. 2006 April;12 (2):75-79.*

Submitted Papers

- J. Honings, H.A. Gaissert, H.F.M. van der Heijden, A.F.T.M. Verhagen, J.H.A.M. Kaanders, H.A.M. Marres. Clinical Aspects and Treatment of Primary Tracheal Malignancies. *(In press, Acta Oto-Laryngologica)*

- L.J. Neeskens, J. Honings, A.J. Beynon, J.P. Lavieille, H.P.M. Kunst. [Retrosigmoidal vestibular neurotomy as treatment for incapacitating vertigo. A case report]. Ned Tijdschr KNO. Dutch title: "Retrosigmoidale neurotomie van de nervus vestibularis als behandeling van invaliderende vertigo. Een case report." *(submitted, Ned Tijdschr KNO)*

Book contributions

- J. Honings, H.A. Gaissert. Chapter 31: Tumors of the Trachea. In: *Textbook on General Thoracic Surgery, to be published by the European Society of Thoracic Surgeons.*

- J. Honings, H.A. Gaissert. Larynx Preserving Resection for Subglottic Tumors. In: Columbus, eds. *Laryngeal Diseases: Symptoms, Diagnosis and Treatment. (To be published by Novascience, 2010)*

- J. Honings & G.J. Halbesma. Chapter 19: Molecular Biology Technology. In: Grisson R and Song JW, eds. *Deja Review: Histology & Medical Cell Biology*. New York, NY: McGraw-Hill; 2006.

Appendix IV

Curriculum Vitae

Jimmie Honings was born in Beuningen, Gld. on September 17th, 1982. He graduated from Dominicus College Nijmegen in 2000 and subsequently started medical school at the Catholic University of Nijmegen (now Radboud University Nijmegen). During his years as an intern, he started a PhD project on tracheal tumors at the Department of Oto-Rhino-Laryngology and Head & Neck Surgery of the Radboud University Nijmegen Medical Centre under the supervision of prof. dr. Henri A. Marres. After finishing medical school and obtaining his medical degree in October 2007, he continued this research project, for which he also worked as a research fellow at the Division of Thoracic Surgery at Massachusetts General Hospital and Harvard Medical School in Boston, MA under the supervision of dr. Henning A. Gaissert. Since April 2009, he is a resident in Oto-Rhino-Laryngology and Head & Neck Surgery with prof. dr. Henri A. Marres.